

Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Agents for the Treatment of Opioid Use Disorder

AFHS classifications: 28:08.12 Opiate Partial Agonists, 28:10 Opiate Antagonists

Buprenorphine (Probuphine, generic)

Buprenorphine plus naloxone (Bunavail, Suboxone, Zubsolv, generic)

Naltrexone (Vivitrol, generic)

Final Report

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Executive Summary

Introduction: Buprenorphine, buprenorphine/naloxone and naltrexone are indicated in the treatment of opioid use disorder (OUD). Eight different formulations are currently available for use in the United States: two buprenorphine products (buprenorphine implant and buprenorphine sublingual tablet), four buprenorphine/naloxone combination products (buprenorphine/naloxone sublingual tablet, buprenorphine/naloxone buccal film, buprenorphine/naloxone sublingual film and buprenorphine/naloxone rapidly dissolving sublingual tablet), and two naltrexone products (naltrexone extended-release injectable suspension and naltrexone hydrochloride tablet).

Opioid abuse and dependence is an increasing concern in the United States and is associated with opioid addiction, overdose deaths, and high societal and medical costs. Opioid use disorder is a chronic and relapsing disease. Treatment involves managing patients through opioid detoxification or induction therapy, and maintenance stages, with many patients needing long-term treatment. A paired pharmacological- psychosocial treatment approach has improved outcomes in both the detoxification and maintenance stages.

According to recent guidelines, pharmacologic treatment options for the treatment of OUD include agonist therapy with methadone, partial agonist therapy with buprenorphine or buprenorphine/naloxone, and antagonist therapy with naltrexone. The American Society of Addiction Medicine (ASAM) guideline published in 2015 does not currently recommend one agent over another in the treatment of OUD because there is limited head-to-head evidence. The Department of Veterans Affairs and Department of Defense (VA/DoD) guideline classifies methadone and buprenorphine/naloxone combination therapy as first-line agents and extended-release naltrexone as a second-line option. No recommendation is provided for oral naltrexone due to insufficient evidence available. For pregnant women, both ASAM and VA/DoD guidelines consider methadone and single-agent buprenorphine as preferred options.

Clinical Efficacy: Five systematic reviews and five randomized controlled trials (RCT) assessing direct head-to head comparisons between the OUD agents containing buprenorphine and naltrexone were identified. The comparative clinical evidence evaluating buprenorphine monotherapy (oral formulations and implant) versus buprenorphine/naloxone combination products or oral naltrexone is limited, and the identified studies presented several weaknesses. In addition, no head-to-head comparisons including extended-release naltrexone are available. The usable findings included the following:

- Two studies directly compared oral buprenorphine monotherapy versus buprenorphine/naloxone rapidly dissolving sublingual tablet for induction therapy. One study (Gunderson 2015) demonstrated non-inferiority in relation to treatment retention rates (primary endpoint). The second study (Webster 2016), containing several limitations, failed to demonstrate non-inferiority for the same endpoint. However, a pooled analysis combining the results from both studies showed similar retention rates between groups. Comparable opioid withdrawals and craving symptoms (secondary endpoints) were reported between groups in the second study.

- One trial demonstrated non-inferiority regarding treatment retention rates between buprenorphine/naloxone rapidly dissolving sublingual tablet and buprenorphine/naloxone sublingual film during the stabilization phase at day 15.
- Buprenorphine implants were non-inferior (in terms of illicit opioid use) to buprenorphine sublingual tablets for maintenance therapy in one trial containing several limitations.
- A Cochrane review with some limitations showed no differences between oral naltrexone and buprenorphine monotherapy for the outcomes of retention and abstinence, with a trend to favor buprenorphine. A recent RCT showed a similar number of days of opioid abstinence between oral naltrexone and buprenorphine/naloxone sublingual. Increased treatment retention was reported in the buprenorphine/naloxone group compared to oral naltrexone group.

Adverse Drug Reactions: Buprenorphine therapy is generally safe, is not usually associated with respiratory depression and, upon abrupt cessation, is associated with a mild withdrawal syndrome. Buprenorphine overdose fatalities have been reported when used parenterally and/or in combination with benzodiazepines. The buprenorphine/naloxone combination products are efficacious in reducing the risk of diversion and abuse. Buprenorphine implant has a Boxed Warning concerning the potential for nerve damage related to the insertion and removal of implants. Naltrexone products are well tolerated. Evidence documenting the poor treatment adherence with oral naltrexone is worrisome. Five patient populations may require special consideration and follow-up when being treated with opioid dependence treatment agents: pediatric patients, geriatric patients, patients with liver disease, pregnant women, and patients with HIV/AIDS.

Risk factors for increased rates of opioid-related serious adverse effects include differences in potency between the agents, prescribing by multiple prescribers or filling at multiple pharmacies, complicated medication regimens, and lack of education and communication between providers and patients.

Summary: Comparative clinical evidence between OUD agents is limited and further research is needed. The main differences between products relate to the mechanism of action (partial agonist versus full antagonist), dosing (daily administration for oral buprenorphine and oral naltrexone products, monthly for extended-release naltrexone and every 6 months for buprenorphine implant), treatment setting (buprenorphine products require a special waiver for physicians and may be provided in an office-based setting or opioid treatment programs while naltrexone can be prescribed in any medical setting without restrictions), requirements for the induction phase (administration of buprenorphine products requires the presence of mild to moderate withdrawal symptoms, which precipitate 8 to 12 hours after last opioid while administration of naltrexone requires patients to be opioid-free for 7-10 days), treatment adherence (poor retention with oral naltrexone), and adverse events. Rates of diversion, physical dependence and stigma are lower with naltrexone compared to buprenorphine products. The selection of an OUD treatment agent should be individualized and guided by the patient's disease history and personal preference in combination with the provider's assessment of the immediate and chronic effects of therapy and overall health status of the patient.

Introduction

Opioids are substances extensively used worldwide for the treatment of pain,¹ cough, and diarrhea.²⁻⁴ Opioid drugs also produce euphoria, sedation, and a feeling of well-being and pleasure.^{3,5} This may lead to abuse and misuse of these substances, causing serious and life-threatening risks such as respiratory depression, physical dependence, addiction, and opioid overdose death.⁵⁻⁸ The number of prescription opioid drug-related overdoses has increased drastically in the United States from 1999 to 2015, increasing awareness of the “national opioid overdose epidemic”.^{8,9} Medical, societal, and criminal-justice costs are significantly increasing due to opioid abuse, misuse, and dependence.¹⁰

Opioid use disorder (OUD), formerly known as opioid dependence, is the term used in the current 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which combine “opioid abuse” and “opioid dependence” criteria from previous DSM versions.⁶ Opioid use disorder is conceptualized as a chronic, relapsing disease^{3,11-13} requiring the management of patients through opioid detoxification or induction therapy, stabilization on an effectively dosed agent, and maintenance therapy. A paired pharmacological- psychosocial treatment approach has improved outcomes in both the detoxification and maintenance stages.¹¹

Treatment of OUD is challenging and often proceeds through a series of remissions and relapses, especially after the detoxification phase.⁶ The goals of therapy are to reduce opioid dependence, decrease morbidity and mortality rates, and improve physical and psychological health, social reintegration and criminal behavior.¹⁴ A number of pharmacologic agents may be used in the treatment of OUD, including methadone, naltrexone, buprenorphine and combinations containing buprenorphine and naloxone. Currently, eight different FDA-approved formulations are available in the United States for the treatment of OUD: generic buprenorphine sublingual tablet,¹⁵ buprenorphine implant (Probuphine),¹⁶ generic buprenorphine/naloxone sublingual tablet,¹⁷ buprenorphine/naloxone buccal film (Bunavail),¹⁸ buprenorphine/naloxone sublingual film (Suboxone),¹⁹ buprenorphine/naloxone rapidly dissolving sublingual tablet (Zubsolv),²⁰ naltrexone extended-release injectable suspension (Vivitrol),²¹ and generic naltrexone hydrochloride tablet.²² This report evaluates the comparative clinical efficacy and safety based on systematic reviews/meta-analyses and randomized controlled trials (RCTs) assessing head-to-head comparisons between the aforementioned products. This report does not address off-label indications for sublingual buprenorphine such as neonatal abstinence syndrome, and those for oral naltrexone such as drug withdrawal, premenstrual syndrome, prophylaxis of morphine adverse reaction and management of self-injurious behavior.²³ Methadone-containing products are not included in this report because the focus is on products that can be provided as office-based therapies. Methadone must be provided through opioid treatment programs (OTP) in highly-structured and specialized methadone clinics.^{6,11,24} Other formulations not discussed in this review include single-ingredient naloxone products indicated for opioid overdose and

buprenorphine products indicated for the management of moderate to severe pain when other alternative options are inadequate (i.e. buprenorphine transdermal system [Butrans], buprenorphine buccal film [Belbuca], buprenorphine injection [Buprenex]).

The buprenorphine (BUP) sublingual (SL) tablet is indicated in the treatment of opioid dependence (for both induction and maintenance phases). It is available in a generic formulation and in two different doses (2 mg and 8 mg). BUP implant was approved in May 2016 by the FDA for maintenance treatment of opioid dependence. Each implant contains 74.2 mg of buprenorphine and the recommended dosage includes four implants that provide a constant low-level dose of buprenorphine for six months. Buprenorphine/naloxone (BUP/NX) buccal film is available in three doses (buprenorphine/naloxone 2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg). BUP/NX SL film is available in four doses (buprenorphine/naloxone 2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg). BUP/NX rapidly dissolving (RD) SL tablet is available in six doses (buprenorphine/naloxone 0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg). A generic sublingual combination tablet formulation is also available in two doses (buprenorphine/naloxone 2/0.5 mg, 8/2 mg). BUP/NX SL film and BUP/NX RD SL tablet are indicated for both induction and maintenance therapy, while BUP/NX buccal film and the generic BUP/NX SL tablet are only approved for maintenance therapy. Naltrexone is available as an extended-release injectable suspension (XR-NTX) and as an immediate-release film-coated tablet formulation (NTX tablet) for the treatment of alcohol dependence and the prevention of relapse in opioid dependence, following opioid detoxification. **Table 1** outlines the available agents, labeled indications and recommended dosages. **Table 2** includes additional information about these agents.

Prior authorization criteria is required for XR-NTX²⁵ and buprenorphine products (buprenorphine monotherapy and buprenorphine/naloxone).²⁶

The following abbreviations are used in this report to refer to the reviewed medications for OUD:

- Buprenorphine sublingual tablet (Generic): Generic BUP SL tablet
- Buprenorphine implant (Probuphine): BUP implant
- Buprenorphine/naloxone buccal film (Bunavail): BUP/NX buccal film
- Buprenorphine/naloxone sublingual tablet (Generic): Generic BUP/NX SL tablet
- Buprenorphine/naloxone rapidly dissolving sublingual tablet (Zubsolv): BUP/NX RD SL tablet
- Buprenorphine/naloxone sublingual film (Suboxone): BUP/NX SL film
- Naltrexone extended-release injectable suspension (Vivitrol): XR-NTX
- Naltrexone hydrochloride film-coated tablet (Generic): Generic NTX tablet

Table 1. FDA Approved Agents for the Treatment of Opioid Dependence^{15-23,27}

Nonproprietary name (Brand Name)	Dosage Forms/Route of Administration	Dosage Strengths	Indication/Dosage Recommendations
Buprenorphine sublingual tablet ¹⁵ (Generics, available since 2009) (Subutex: discontinued)	Sublingual tablets	2 mg, 8 mg buprenorphine	Treatment of opioid dependence Induction therapy: One tablet /day <ul style="list-style-type: none"> • Day 1: 8 mg • Day 2 and subsequent induction days: 16 mg (usual induction dosage range: 12 to 16 mg/day) Maintenance therapy: <ul style="list-style-type: none"> • Target dose: 16 mg/day (in some patients 12 mg/day may be effective) • Range: 4-24 mg/day*
Buprenorphine implant (Probuphine) ¹⁶ Approval date: May 2016	Implant for subdermal administration	One implant contains 74.2mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride)	Maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine containing product (≤ 8 mg/day) <ul style="list-style-type: none"> • Not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent Dosage Recommendations: <ul style="list-style-type: none"> • 4 implants inserted subdermally in the upper arm for 6 months of treatment • Remove no later than 6 months after the date of insertion; if continued treatment is desired, insert 4 new implants subdermally in the inner side of the contralateral arm. After one insertion in each arm, discontinue treatment with subdermal implants. • Converting back to sublingual tablet: On day of implant removal, resume buprenorphine treatment at previous sublingual dose

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Nonproprietary name (Brand Name)	Dosage Forms/Route of Administration	Dosage Strengths	Indication/Dosage Recommendations
Buprenorphine/naloxone buccal film (Bunavail) ¹⁸ Approval date: June 2014	Buccal film	Buprenorphine/naloxone: Bunavail: 2.1 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg	Maintenance treatment of opioid dependence <u>Target dose:</u> 8.4 mg buprenorphine/ naloxone 1.4 mg once daily; dosage should be adjusted in increments/decrements of buprenorphine 2.1 mg/naloxone 0.3 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms <u>Usual range:</u> Buprenorphine 2.1 to 12.6 mg/naloxone 0.3 to 2.1 mg once daily
Buprenorphine/naloxone sublingual tablet ¹⁷ (Generics, available since 2013) (Suboxone sublingual tablets: Discontinued)	Sublingual tablets	Buprenorphine/naloxone: Generic: 2 mg/0.5 mg 8 mg/2 mg	Maintenance treatment of opioid dependence <u>Target dose:</u> 16 mg/4 mg buprenorphine/naloxone once daily Dosage should be adjusted in increments/decrements of buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms <u>Usual range:</u> Buprenorphine 4 to 24 mg/naloxone 1 to 6 mg once daily*

Table 1. FDA Approved Agents for the Treatment of Opioid Dependence^{15-23,27}

Nonproprietary name (Brand Name)	Dosage Forms/Route of Administration	Dosage Strengths	Indication/Dosage Recommendations
Buprenorphine/naloxone sublingual tablets (Zubsolv) ²⁰ Approval date: March 2013	Rapidly dissolving sublingual tablets	Buprenorphine/naloxone: 0.7 mg/0.18 mg 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Treatment of opioid dependence Induction (only for heroin or other short-acting opioid dependency): <u>Day 1:</u> Start with buprenorphine 1.4 mg/naloxone 0.36 mg; may titrate dose, based on control of acute withdrawal symptoms in increments of buprenorphine 1.4 mg/naloxone 0.36 mg or buprenorphine 2.9 mg/naloxone 0.71 mg every 1.5 to 2 hours to a total day 1 dose <u>up to buprenorphine 5.7 mg/naloxone 1.4 mg</u> . Some patients (eg, those with recent exposure to buprenorphine) may tolerate up to buprenorphine 4.2 mg/naloxone 1.08 mg as a single, second dose. <u>Day 2:</u> Up to buprenorphine 11.4 mg/naloxone 2.9 mg once daily Maintenance: <u>Target dose:</u> Buprenorphine 11.4 mg/naloxone 2.9 mg once daily Dosage should be adjusted in increments/decrements of buprenorphine 1.4 mg/naloxone 0.36 or buprenorphine 2.9 mg/naloxone 0.71 mg to a level that maintains treatment and suppresses opioid withdrawal symptoms <u>Usual range:</u> Buprenorphine 2.9 to 17.2 mg/naloxone 0.71 to 4.2 mg once daily
Buprenorphine/naloxone sublingual film (Suboxone) ¹⁹ Approval date: August 2010	Sublingual film (sublingual or buccal administration)	Buprenorphine/Naloxone: 2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Treatment of opioid dependence Induction: <u>Day 1:</u> start with buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg; may titrate dose, based on control of acute withdrawal symptoms, in buprenorphine 2 mg/naloxone 0.5 mg or buprenorphine 4 mg/naloxone 1 mg increments approximately every 2 hours <u>up to a total dose of buprenorphine 8 mg/naloxone 2 mg</u> . <u>Day 2:</u> Up to buprenorphine 16 mg/naloxone 4 mg once daily. Maintenance: <u>Target dose:</u> Buprenorphine 16 mg/naloxone 4 mg once daily; Dosage should be adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that maintains treatment and suppresses opioid withdrawal symptoms <u>Usual range:</u> Buprenorphine 4 to 24 mg/naloxone 1 to 6 mg once daily*

Table 1. FDA Approved Agents for the Treatment of Opioid Dependence^{15-23,27}

Nonproprietary name (Brand Name)	Dosage Forms/Route of Administration	Dosage Strengths	Indication/Dosage Recommendations
Naltrexone extended-release injectable suspension (Vivitrol) ²¹ Approval date: April 2006	<ul style="list-style-type: none"> Extended-release injectable powder for suspension for single use Intramuscular use 	Naltrexone: 380 mg/vial	1. Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol. Patients should not be actively drinking at the time of initial Vivitrol administration 2. Prevention of relapse to opioid dependence, following opioid detoxification <u>Dosage Recommendations:</u> <ul style="list-style-type: none"> Naltrexone 380 mg delivered intramuscularly every 4 weeks or once a month. <i>Note:</i> Prior to initiating Vivitrol, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization
Naltrexone hydrochloride film-coated tablet ²² (Generic, available since 1998)	Oral film-coated tablet	Naltrexone hydrochloride: 50 mg	1. Treatment of alcohol dependence 2. Blockade of the effects of exogenously administered opioids Naltrexone Hydrochloride tablets have not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions <u>Dosage Recommendations:</u> <ul style="list-style-type: none"> Initial dose: 25 mg. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter <i>Note:</i> Prior to initiating naltrexone, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to reduce the risk of precipitated withdrawal in patients dependent on opioids, or exacerbation of a preexisting subclinical withdrawal syndrome. <u>Unlabeled indications:</u> <ul style="list-style-type: none"> Drug withdrawal Morphine adverse reaction; Prophylaxis Premenstrual syndrome Self-injurious behavior Cholestatic pruritus (adults)

Notes:

- These medicines should be used as part of a complete treatment plan to include counseling and psychosocial support
- See pharmacology section for further information about the equivalency between buprenorphine/naloxone formulations
- Dosages higher than 24 mg buprenorphine per day and 24 mg/6 mg buprenorphine/naloxone per day have not been demonstrated to provide a clinical advantage^{15,19}

Table 2. Additional Characteristics of Opioid Use Disorder Medications^{2,6,15-22}

Agents		Mechanism of action	Setting/Restrictions	Induction Therapy*	Maintenance Therapy*	REMS Program
BUPRENORPHINE	Buprenorphine sublingual tablet	Mu-opioid receptor partial agonist	<ul style="list-style-type: none">OBOT, home-based setting or supervised OTPTreatment physicians should have special training and certificationTreatment should start when patients experience mild to moderate opioid withdrawal	Yes (for patients on methadone or long-acting opioids; or those on heroin or short-acting opioid products)	Yes	Yes
	Buprenorphine implant		<ul style="list-style-type: none">Treatment should be used as part of a complete treatment plan to include counseling and psychosocial supportBuprenorphine implant: Implants should be inserted and removed by health care providers trained and certified through the Probuphine REMS program	No	Yes	Yes
BUPRENORPHINE/NALOXONE	Buprenorphine/naloxone sublingual tablet	Buprenorphine: Mu-opioid receptor partial agonist	<ul style="list-style-type: none">OBOT, home-based setting or supervised OTPTreatment physicians with special training and certification	No	Yes	Yes
	Buprenorphine/naloxone buccal film (Bunavail)	Naloxone: Mu-opioid receptor antagonist (added to buprenorphine to discourage intravenous buprenorphine misuse)	<ul style="list-style-type: none">Treatment should start when patients experience mild to moderate opioid withdrawal	Yes (for patients on heroin or short-acting opioid products)	Yes	Yes
	Buprenorphine/naloxone sublingual tablet (Zubsolv)		<ul style="list-style-type: none">Treatment should be used as part of a complete treatment plan to include counseling and psychosocial support			
	Buprenorphine/naloxone sublingual film (Suboxone)			Yes (for patients on heroin or short-acting opioid products)	Yes	Yes

NALTREXONE	Naltrexone extended-release (Vivitrol)	Mu-opioid receptor antagonist	<ul style="list-style-type: none"> Prescribed in any setting by any clinician with the authority to prescribe any medication Patients must be opioid-free for 7–10 days 	No	Yes	Yes
	Naltrexone hydrochloride (oral tablet)		<ul style="list-style-type: none"> Injectable naltrexone should be administered in an office with a clinician trained through the Vivitrol REMS program Treatment should be used as part of a complete treatment plan to include counseling and psychosocial support 	No	Yes	No

Abbreviations: REMS; risk evaluation and mitigation strategy, OBOT, office-based opioid treatment; OTP, opioid treatment program

* Package insert indications

Notes:^{15,18-20}

1. Buprenorphine hydrochloride sublingual tablets contain no naloxone hydrochloride and are preferred for use **only during induction**.¹⁵ To avoid precipitating withdrawal, induction with buprenorphine hydrochloride sublingual tablets should be undertaken when objective and clear signs of withdrawal are evident.
 - **Patients dependent on heroin or other short-acting opioids:**
 - Buprenorphine/naloxone sublingual or buprenorphine monotherapy can be administered for induction therapy.
 - The first dose of buprenorphine/naloxone sublingual or buprenorphine should be administered when objective signs of moderate opioid withdrawal appear, and not less than 6 hours after the patient last used an opioid.
 - **Patients dependent on methadone or other long-acting opioids:**
 - Buprenorphine monotherapy is preferred. Buprenorphine/naloxone contains naloxone, which is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal. For this reason, buprenorphine monotherapy is recommended in patients taking long-acting opioids when used according to approved administration instructions.
2. Buprenorphine/naloxone is preferred over buprenorphine monotherapy for **maintenance and unsupervised therapy**. Use buprenorphine monotherapy in pregnant women and in patients that cannot tolerate naloxone.^{17,19}

Utah Medicaid Utilization Data

According to Utah Medicaid fee-for-service (FFS) data, the number of unique FFS and Accountable Care Organization (ACO) patients with only opioid dependence diagnosis coding (using both ICD-9 and ICD-10) from 2014 to 2017 was 14,252 (8,289 ACO and FFS patients and 3,237 FFS patients in 2016). The number of unique patients with both opioid and alcohol dependence diagnosis coding was 3,202 from 2014 to 2017 (1,197 ACO and FFS patients and 566 FFS patients in 2016). Combining data from both FFS and ACO payers, the most commonly prescribed opioid dependence treatment agent during 2016 was BUP/NX SL film, followed by generic NTX oral tablet, generic BUP SL tablet, BUP/NX RD SL tablet and XR-NTX. There were limited claims for generic BUP/NX SL tablet and BUP/NX buccal film. No utilization data was reported for BUP implant during 2016 and only 1 patient was on treatment with BUP implant in 2017. **Table 3** contains ACO and FFS number of claims and patients for 2016.

Table 3. 2016 Utah Utilization Data for Opioid Use Disorder Agents

Agents (brand name)	2016 ACO and FFS Claims	2016 ACO and FFS Patients
BUP/NX SL film (Suboxone)	4411	640
Generic NTX tablet	1201*	353*
Generic BUP SL tablet	385	76
BUP/NX RD SL Tablet (Zubsolv)	248	39
XR-NTX (Vivitrol)	136*	38*
Generic BUP/NX SL tablet	14	12
BUP/NX buccal film (Bunavail)	5	2

Abbreviations: ACO, accountable care organizations; FFS, fee-for-service

* Naltrexone products are also indicated for alcohol dependence

It is of note that naltrexone is indicated for both opioid and alcohol dependence. In 2016, among the 38 FFS and ACO patients on treatment with XR-NTX, 27 unique patients had opioid dependence diagnosis coding and 7 patients had both opioid and alcohol dependence diagnosis coding. Likewise, among 353 FFS and ACO patients on treatment with NTX oral tablets, 122 unique patients had opioid dependence diagnosis coding and 50 patients had both opioid and alcohol dependence diagnosis coding.

The Utah Medicaid Preferred Drug List (PDL) currently includes BUP/NX SL film as the preferred agent in the substance-abuse treatment category. BUP/NX buccal film, BUP/NX RD SL Tablet, generic buprenorphine and generic buprenorphine/naloxone are non-preferred options.²⁸

Disease Overview

OUD is a chronic disease leading to impairment, distress and relapses.^{6,29} According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a patient is diagnosed with an OUD if at least 2 of the following 11 symptoms specified by DSM-5 are present within a 12-month period.^{6,29}

Diagnostic Criteria for Opioid Use Disorder^{6,29}

1. Opioids are often taken in larger amounts or over a longer period than was intended.
 2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use
 3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
 4. Craving, or a strong desire or urge to use opioids.
 5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
 6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
 7. Important social, occupational, or recreational activities are given up or reduced because of opioid use
 8. Recurrent opioid use in situations in which it is physically hazardous.
 9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
 10. Tolerance, including need for increased amounts of opioids or diminished effect with continued use at the same amount – as long as the patient is not taking opioids under medical supervision
 11. Withdrawal manifested by characteristic opioid withdrawal syndrome or taking opioids to relieve or avoid withdrawal symptoms – as long as the patient is not taking opioids under medical supervision.
-

Severity of OUD is classified as mild (presence of 2-3 symptoms), moderate (presence of 4-5 symptoms), or severe (presence of 6 or more symptoms).⁶

The American Society of Addiction Medicine (ASAM) guideline^{6,30} recommends the evaluation of a patient with suspected OUD considering the patient's medical history, physical assessment, laboratory tests (e.g. urine drug testing), mental health status, and social and environmental factors. The common intoxication and withdrawal signs can be measured using different scales such as the clinical opioid withdrawal scale (COWS) and the subjective opioid withdrawal scale (SOWS). Populations at risk of opioid misuse or abuse include patients with a history of personal and family substance abuse, young patients, and those with a history of mental illnesses.³¹ There are several tools to assess the risk of misuse or abuse before starting treatment with opioids for chronic pain.³²

OUD is associated with high rates of mortality, morbidity, and disease transmission.³³ It is also associated with increased costs related to health care, crime, law enforcement, family distress, and loss of productivity. Hence, the management of OUDs is essential to reduce healthcare costs and to improve the overall well-being of the patients and families affected.

Regarding mortality rates, from 1999 to 2015 drug overdose-related deaths have quadrupled and more than 183,000 Americans have died due to prescription opioid overdose.³⁴ It is estimated that 91 Americans die every day due to opioid overdose.³⁵ From 2014 to 2015,

deaths due to opioid overdose increased by 15.6%. In 2015, 33,091 (63.1%) out of 52,404 drug overdose deaths were caused by an opioid (including illicit manufactured fentanyl, heroin and natural/semisynthetic opioids like morphine, codeine, oxycodone, hydrocodone, hydromorphone and oxymorphone), and nearly half of the opioid overdose deaths were caused by prescription opioids (principally methadone, oxycodone, and hydrocodone).^{34,36} Deaths associated with methadone use decreased by 9.1% due to the implementation of safety measures to prevent its improper use.^{36,37} The Centers for Disease Control and Prevention (CDC) states that the number of prescription painkiller overdose deaths is now greater than deaths from heroin and cocaine combined.¹⁴ Opioid overdose deaths now exceed deaths resulting from automobile crashes in the US.³⁸

In Utah, there has been an alarming increase in deaths related to misuse of opioid prescription drugs, which began to increase substantially in 2001, peaked in 2007 and then decreased through 2010.³⁹ In 2005, Utah had the highest rates in the nation of reported nonmedical use of pain relievers and increase in prescription opioid-related deaths.⁴⁰ According to 2015 data from the Utah Department of Health, 24 Utahns die every month due to prescription opioid overdoses (mainly caused by oxycodone and methadone).³⁹ From 2013 to 2015, Utah ranked 7th in the US in drug overdose deaths.³⁹

Regarding opioid prescription rates in the US, the number of prescriptions continues to be high. From 1999 to 2014, prescription opioid sales increased significantly (four-fold) without any significant change in the quantity of people suffering from pain.⁴¹ Retail opioid prescription rates peaked in 2012 (81.3 per 100 US residents) and then decreased to 66.5 per 100 US residents in 2016.⁴¹

In Utah, preventative strategies such as the Utah Controlled Substance Database Program, which provides prescribers and pharmacists with opioid-prescription fill histories, were implemented to curb inappropriate prescribing. In addition, federal and state-level guidelines were published to promote judicious prescribing practices and minimize the risk of abuse.^{42,43} Hence, the number of opioid prescriptions per 100 Utahns decreased from 84.5 in 2012 to 70.4 in 2016.⁴⁴

Groups that are more likely to use prescription opioids include adults of 40 years or older, women, and non-Hispanic whites.⁴¹ People that abuse or are at highest risk of overdose may get opioids from a friend or relative (buying or stealing them, or for free), from different prescribers, or buying from a drug dealer or other stranger.⁴¹

Pharmacologic Treatments for Opioid Use Disorders

*“Medication-assisted treatment (MAT) is a comprehensive approach that combines approved medications (currently, methadone, buprenorphine or naltrexone) with counseling and other behavioral therapies to treat patients with opioid use disorder.”*⁴⁵ MAT has been shown to

decrease morbidity and mortality rates, overdose deaths, disease transmission, criminal activity, and improve treatment adherence and social environment.^{46,47} Guidelines and health organizations recommend opioid abuse treatment.⁴⁸ One of the measures included in the FDA's opioid action plan emphasizes the increased use and availability of MAT.⁴⁹

Treatment of opioid-related disorders may occur in different practice settings including inpatient hospitals, outpatient clinics, opioid treatment centers, self-help programs, therapeutic communities, and physicians' offices.⁵⁰ The choice of setting is determined by the individual patient's clinical characteristics, treatment needs and treatment preferences. An opioid overdose or initial detoxification should generally be managed in a supervised medical setting while maintenance therapy and psychosocial treatments may be carried out in outpatient clinics, centers and physicians' offices.⁵⁰⁻⁵²

Methadone is an opioid analgesic with unique features, including a slow onset of action and long elimination half-life, which makes it an effective treatment option for both detoxification and long-term treatment of OUD. However, methadone therapy is associated with unpredictable dosing patterns and increased risk of cardiac arrhythmias.⁵³ Methadone treatment for OUD should only be performed in a highly structured methadone clinics and through specially licensed opioid treatment programs (OTP).⁶

Buprenorphine is a partial opioid agonist with weaker effects than those of full opioids such as heroin and methadone. It has long duration of action, which also makes it an effective treatment option for both detoxification and long-term treatment of OUD.^{33,54} Buprenorphine for the treatment of OUD can be prescribed or dispensed by qualified US physicians (required to acquire and maintain certifications to legally dispense opioid dependency medications) in an office-based opioid treatment [OBOT]⁶ (under the Drug Addiction Treatment act of 2000/DATA 2000; refer to appendix 5 Buprenorphine Waiver Management), or in opioid treatment programs [OTPs] similar to methadone OTPs.⁵⁴ The OBOT setting has increased patients' accessibility to partial agonists. The number of patients that received buprenorphine via OTPs increased from 727 (in 2004) to 7,020 (in 2011) in the US.^{55,56} Patients that received it via non-OTP increased from 1670 (in 2004) to 25,656 (in 2011).^{55,56} Buprenorphine treatment consists of three phases: induction, stabilization, and maintenance. For induction (lasting 1 to 3 days), the patient must be free of opioids for 12 to 24 hours and should experience mild to moderate withdrawal symptoms before starting induction therapy. The objective of this phase is to find a minimum dose of buprenorphine where no craving and no withdrawal symptoms appear. During stabilization, the buprenorphine dose is adjusted such that cravings and side-effects dissipate. Patients continue to the maintenance phase, in which they receive treatment with buprenorphine and psychosocial support long-term.^{8,57}

Naltrexone and naloxone are opioid antagonists. Naltrexone is used in the treatment of opioid dependence only after the patient has been opioid-free for at least 7-10 days to avoid

precipitating withdrawal symptoms.²¹ Naltrexone is not associated with physical dependence, diversion, or additive CNS depression. However, it is associated with withdrawal symptoms, increased rates of opioid sensitivity, and an increased risk for overdose with opioid use upon discontinuation of therapy.⁵⁰ The oral formulation of naltrexone has been available since the 1980's and is dosed once every day or every other day. Historically, naltrexone therapy is associated with poor compliance⁵⁸ and high drop-out rates with the oral regimen, “with over one-quarter dropping out after a few days and almost one-half dropping out in [the] first few weeks.”⁵⁹ However, in cohorts compliant with oral naltrexone, positive outcomes have been demonstrated including lower relapse rates and improvements in employment, legal, and social status.⁵⁹ These results motivated the development of XR-NTX, approved for OUD in 2010. XR-NTX addresses the adherence concern with intramuscular administration every 4 weeks. Naltrexone prescriptions can be filled by retail pharmacies and issued by prescribers without a special waiver or registration number from the Drug Enforcement Agency (DEA).⁶

Naloxone is another pure opioid antagonist. It is used as an antidote in opioid overdose. When added to buprenorphine, naloxone reduces the ability to abuse buprenorphine. Naloxone is not well absorbed when administered sublingually. However, administered parenterally, naloxone will replace buprenorphine at the opioid receptor site. The parenteral administration of buprenorphine plus naloxone will produce a withdrawal syndrome.

Clinical Guidelines

Table 3 contains a summary of the most recent clinical guideline recommendations for the treatment of OUDs.

The American Society of Addiction Medicine (ASAM) treatment guideline⁶ does not specify preference for one product over another for OUD due to limited head-to-head evidence.⁶ Physicians should select buprenorphine, methadone, or naltrexone based on patient's preference, treatment history, and facility type. Oral naltrexone should only be considered if supervision is available and patients are highly motivated.⁶ In contrast, the Department of Veterans Affairs and Department of Defense (VA/DoD) guideline⁶⁰ concludes that there is strong evidence supporting opioid agonist therapy and moderate evidence supporting extended-release naltrexone (XR-NTX) for relapse prevention. Methadone and buprenorphine/naloxone combination therapy are designated as first-line agents and XR-NTX as a second-line option for patients unwilling to take or who have failed opioid agonist therapies, patients with contraindications, or individuals without access to preferred options. No recommendations are suggested for oral naltrexone in OUD due to the limited amount of evidence. Similar preferences to those included in the VA/DoD guideline are stated by the World Federation of Societies of Biological Psychiatry.^{51,60}

Both ASAM and VA/DoD guidelines consider methadone and buprenorphine alone as preferred options for pregnant women. Limited evidence in this subgroup is available for

buprenorphine and naloxone combination products, so they are not recommended during pregnancy.⁶

Guidelines overwhelmingly suggest that treatment should be individualized. Selection of the appropriate regimen and treatment facility should be guided by the patient's disease history and preferences, along with the provider's assessment of the patient's psychosocial condition, co-occurring disorders, opportunities for treatment retention, and risk of medication diversion.^{11,50,51,60} The ASAM guideline does not recommend a specific length of treatment regarding each agent; however, it highlights that relapse rates are high for most patients. Thus, long-term treatment is often needed and the treatment and duration should be based on the prescriber's assessment of the patient's response and circumstances.¹¹ A similar recommendation is made by other experts.^{19,60}

Apart from the recommendations reported in clinical guidelines, it is known that buprenorphine monotherapy has the potential for abuse and may not be appropriate for long-term opioid dependence. Instead, buprenorphine/naloxone combination products can help mitigate the abuse potential and may be adequate options for long-term opioid dependence therapy.⁶¹

Product labeling also suggests some treatment preferences. Buprenorphine alone is the preferred choice for induction therapy in patients physically dependent on methadone or long-acting opioids.¹⁵ Buprenorphine/naloxone products are not recommended in this type of patient, as the medications may increase the risk and severity of withdrawal symptoms.³³ Buprenorphine/naloxone or buprenorphine alone may be used for initial induction therapy in patients physically dependent on heroin or short-acting opioid products.¹⁹ After induction, buprenorphine/naloxone products are preferred for unsupervised maintenance therapy.¹⁹ In pregnant women and patients with any allergy to naloxone, the use of buprenorphine alone is recommended.¹⁵

Table 4. Guidelines for the Management of Opioid Dependence

Guideline	Recommendations
CDC Guideline for Prescribing Opioids for Chronic Pain (2016) ⁴²	“Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.” ⁴²
American Society of Addiction Medicine (ASAM), “National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use” (2015) ^{48,62}	<p>⇒ “Clinicians should consider the patient’s preferences, past treatment history, and treatment setting when deciding between the use of <u>methadone, buprenorphine, and naltrexone</u> in the treatment of addiction involving opioid use.”</p> <p>⇒ “The venue in which treatment is provided is as important as the specific medication selected.</p> <ul style="list-style-type: none"> ○ Opioid Treatment Programs (OTP) offer daily supervised dosing of methadone, and increasingly of buprenorphine. ○ Naltrexone can be prescribed in any setting by any clinician with the authority to prescribe any medication. ○ In accordance with federal law (21 CFR §1306.07), Office-Based Opioid Treatment (OBOT), which provides medication on a prescribed weekly or monthly basis, is limited to buprenorphine. ○ Clinicians should consider a patient’s psychosocial situation, co-occurring disorders, and risk of diversion when determining whether Opioid Treatment Programs (OTP) or OBOT is most appropriate.” <p>⇒ “Methadone is recommended for patients who may benefit from daily dosing and supervision in an OTP, or for patients for whom buprenorphine for the treatment of OUD has been used unsuccessfully in an OTP or OBOT setting.”</p> <p>⇒ “Oral <u>naltrexone</u> for the treatment of OUD is often adversely affected by poor medication adherence.</p> <ul style="list-style-type: none"> ○ Clinicians should reserve its use for patients who would be able to comply with special techniques to enhance their adherence; e.g. observed dosing. <u>Extended-release injectable naltrexone</u> reduces, but does not eliminate, issues with medication adherence.” ○ “The prescribing of benzodiazepines or other sedative-hypnotics should be used with extreme caution in patients who are prescribed methadone or buprenorphine for the treatment of OUD.” <p><i>Special Populations with OUD (refer to guidelines for additional information)</i></p> <p>⇒ Pregnant women:</p> <ul style="list-style-type: none"> - “Pregnant women who are physically dependent on opioids should receive treatment using <u>methadone or buprenorphine monoproduct</u> rather than withdrawal management or abstinence.” - “There is insufficient evidence to recommend the combination <u>buprenorphine/naloxone combination</u>.” - “Treatment with methadone should be initiated as early as possible during pregnancy.” - “If a women becomes pregnant while she is receiving naltrexone, it is appropriate to discontinue if the patient and doctor agree that the risk of relapse is low.” - Naloxone is NOT recommended (unless life threatening overdose) - “Mothers receiving methadone and buprenorphine monoproduct for the treatment of OUDs should be encouraged to breastfeed.” - “Dose increases as pregnancy advances” <p>⇒ Individuals with pain:</p> <ul style="list-style-type: none"> - “NSAIDs or acetaminophen should be tried first” - Increase dosing of mu-opioid agonists (methadone or buprenorphine) or add opioid - Severe acute pain: Discontinue buprenorphine; add high potency opioid (fentanyl).” <p>⇒ Surgery:</p> <ul style="list-style-type: none"> - Discontinue oral naltrexone 72 hours (or 30 days for extended-release naltrexone) before surgery.

	<ul style="list-style-type: none"> - Discontinue buprenorphine 24–36 hours before surgery <p>⇒ Adolescents:</p> <ul style="list-style-type: none"> - Although FDA approval of these agents is limited in regard to patients under age 18, the guideline advocates that practitioners should consider employing pharmacotherapy for adolescents with OUD. <p>⇒ Individuals in the Criminal Justice System:</p> <p>“There is insufficient evidence to recommend any one treatment as superior to another for prisoners or parolees.” Only naltrexone XR is recommended (as antagonist) and not oral naltrexone. “Pharmacotherapy should be initiated a minimum of 30 days prior to release from prison.”</p> <p>NOTE: “On July 6, 2016, the Department of Health and Human Services (HHS) announced that it will raise the limit on the number of patients that can receive the addiction medicine buprenorphine to 275 patients per qualified provider.⁶³ Previously, physicians were limited to treatment of 100 patients.”⁶⁴</p>
VA/DoD clinical practice guideline for the management of substance use disorders (2015)⁶⁰	<p style="text-align: center;"><i>Pharmacotherapy for OUD</i></p> <p>⇒ For patients with opioid use disorder, the Work Group recommends offering one of the following medications, considering patient preferences:</p> <ul style="list-style-type: none"> • Buprenorphine/naloxone combination therapy • Methadone in an opioid treatment program (OTP) <p>⇒ In <u>pregnant women</u> with OUD for whom buprenorphine is selected, the Work Group suggests offering buprenorphine alone (i.e., without naloxone) considering patient preferences</p> <p>⇒ For patients with OUD for whom buprenorphine is indicated, the Work Group recommends individualizing choice of appropriate treatment setting (i.e. opioid treatment program or office-based) considering patient preferences.</p> <p>⇒ For patients with OUD for whom <u>opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued</u> and who have established abstinence for a sufficient period of time (see narrative in the original guideline document), the Work Group recommends offering</p> <ul style="list-style-type: none"> • Extended-release injectable naltrexone <p>⇒ There is insufficient evidence to recommend for or against oral naltrexone for treatment of OUD</p> <p style="text-align: center;"><i>Psychosocial Interventions with or without Pharmacotherapy</i></p> <ul style="list-style-type: none"> - For patients in office-based buprenorphine treatment, there is insufficient evidence to recommend for or against any specific psychosocial interventions in addition to addiction-focused medical management. Choice of psychosocial intervention should be made considering patient preferences and provider training/competence. <p>⇒ In opioid treatment program settings, the Work Group suggest offering individual counseling and/or contingency management, considering patient preferences and provider training/competence.</p> <p>⇒ For patients with opioid use disorder for whom opioid use disorder pharmacotherapy is contraindicated, unacceptable or unavailable, there is insufficient evidence to recommend for or against any specific psychosocial interventions.”⁶⁰</p>
National Institute on Drug Abuse: Principles of Drug Addiction Treatment: A Research-Based Guide (Third Edition; 2012)⁶⁵	<p style="text-align: center;"><i>Pharmacotherapies for opioid addiction:</i></p> <p>No single treatment (methadone, buprenorphine or buprenorphine/naloxone) is appropriate for everyone and depends on the type of drug and characteristics of the patient.</p> <p>“Effective treatment attends to multiple needs of the individual, not just his or her drug abuse. To be effective, treatment must address the individual’s drug abuse and any associated medical, psychological, social, vocational, and legal problems. It is also important that treatment be appropriate to the individual’s age, gender, ethnicity, and culture.”</p>

	<p>“Remaining in treatment for an adequate period of time is critical.” Appropriate duration depends on type and degree of patient’s problems and needs; research indicates at least 3 months for most (to significantly reduce or stop drug use); frequently requires multiple treatment episodes (long-term process); relapses can occur (treatment needs to be reinstated or adjusted); programs should include strategies to engage and keep patients in treatment (to prevent leaving treatment too early).</p>
<p>The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. (2011)⁵¹</p>	<p>⇒ <u>First-line medications</u>: methadone, buprenorphine or buprenorphine/naloxone</p> <p>⇒ <u>Second-line medications</u>: heroin, naltrexone</p> <p>⇒ <u>Adjunctive medications</u>: clonidine, lofexidine (unavailable in the US)</p>
<p>Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009)⁶⁶</p>	<p>⇒ <u>First-line treatment recommendations</u>: Opioid agonist combined with psychosocial assistance</p> <p>⇒ <u>Second-line treatment options</u>: naltrexone (it may be useful in preventing relapse in patients who have withdrawn from opioids and are highly motivated to abstain from opioid use)</p> <p>⇒ <u>Opioid agonists include</u>: oral methadone liquid, sublingual buprenorphine (both medications provide good outcomes; methadone may be recommended over buprenorphine, as it is more effective and costs less; buprenorphine may be more appropriate for patients in whom methadone is unwanted, inappropriate or ineffective)</p>
<p>American Psychiatric Association Practice Guideline for the Treatment of Patients With Substance Use Disorders, Second Edition (2006)⁵⁰</p>	<p><u>Maintenance treatment</u> in patients with a prolonged history (>1 year): methadone, buprenorphine, behavioral therapies, counseling</p>
<p>Clinical Guidelines for the use of Buprenorphine in the Treatment of Opioid Addiction (CSAT 2005)^{67,68}</p> <p>Quick Guide for Physicians Based on TIP 40 Clinical Guidelines for the use of Buprenorphine treatment in the Treatment of Opioid Addiction⁶⁸</p>	<p>Buprenorphine can be used for:</p> <p>⇒ <u>Long-term maintenance</u>: “Appropriate dosages of buprenorphine are more effective than low dosages (20–35 mg) of methadone. A buprenorphine dosage of 8–16 mg/day is equivalent to about 60 mg/day of methadone.” Refer to guidelines for additional information</p> <p>“Conditions and Circumstances That May Preclude a Patient as a Candidate for Office-Based Buprenorphine Treatment</p> <ul style="list-style-type: none"> • Co-occurring dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol) • Significant untreated co-occurring mental disorders • Active or chronic suicidal or homicidal ideation or attempts • Poor response to previous well-conducted attempts at buprenorphine treatment • Significant medical complications.” <p>⇒ <u>Induction</u>: Day 1 should not exceed 8 mg. Patients who were on LA opioids (e.g. methadone) should be managed by physicians experienced with the procedure. Day 2 switch to buprenorphine/naloxone combination (if day 1 was monotherapy and patient is not pregnant).”</p> <p>⇒ <u>Stabilization</u> (1-2 months; physicians see patients at least weekly): Adjustment of doses. “<u>Nearly all patient stabilize on daily doses of 16/4-24/6 mg; some may require up to 32/8 mg daily.</u>” Once a stable dose has been reached and patient stopped using illicit drugs, biweekly or monthly visits may be appropriate.</p> <p>⇒ <u>Maintenance</u> (may be indefinitely or relatively short): “Longer maintenance treatment is associated with less illicit drug use and fewer complications.”</p> <p><u>“Long-term medication management.</u> The design of long-term treatment depends on the patient’s treatment goals and on objective signs of treatment success. After a patient is stabilized successfully, decisions to decrease or discontinue buprenorphine should be based on the patient’s desire and commitment to become medication free and on the physician’s confidence that tapering will be successful.”</p>

Patient Management

"Pharmacotherapy is rarely sufficient treatment for substance dependence. Physicians should refer patients for psychosocial services. Substance abuse counseling and participation in a mutual-help group are necessary for most patients. DATA 2000 stipulates that physicians must have the capacity to refer patients for appropriate counseling and other nonpharmacological therapies.

Patients and physicians should agree on treatment goals and devise a treatment plan. The plan should specify conditions that will result in treatment termination and contingencies for treatment failure."

⇒ Monthly toxicology tests (usually urine screening)

SPECIAL POPULATIONS

⇒ **Co-occurring medical problems:** *"Treating opioid addiction in patients with co-occurring medical conditions is likely to result in better outcomes for the co-occurring conditions than would be achieved if the opioid use were not treated."*

⇒ **Pregnancy:** *"Methadone is the standard treatment for pregnant women who are addicted to opioids. Few studies exist on the use of buprenorphine in pregnant women. Buprenorphine is a Category C agent, which means that the benefits of using the drug in pregnant women may be acceptable despite the risk of adverse effects on the fetus."*

⇒ **Adolescents and Young Adults:** Buprenorphine may be preferred to methadone because of relative ease of withdrawal (physicians should be familiar with State laws regarding parental consent).

⇒ **Elderly Patients:** Limited evidence; caution advised especially during induction (metabolism and absorption differences)

⇒ **Patients with co-occurring mental disorders:** Assess these before or during initiation of buprenorphine treatment; refer patients with polysubstance abuse for treatment of their other addictions.

⇒ **Patients with pain:** First non-opioid analgesics; if not relieved, SA opioids can be considered & discontinue buprenorphine; follow induction guidelines to restart buprenorphine.

⇒ **Patients discharged from controlled environments/ involuntary detoxification** (released from prison or return from extended stays in countries where illicit opioids are difficult to obtain): "Patient assessment should determine the diagnosis of opioid dependence or addiction and the risk of the patient's returning to an addiction lifestyle."

⇒ **Health Care Professionals Who are Addicted to Opioids:** "Buprenorphine may be an appropriate treatment option for healthcare professionals but should be part of a comprehensive, monitored recovery plan."

Abbreviations: ASAM, American Society of Addiction Medicine; OBOT, office-based opioid treatment; OTP, opioid treatment program; OUD, opioid use disorder;

Pharmacology

The opioid analgesics bind to specific receptors within and outside the central nervous system (CNS).^{69,70} Three opioid receptors mediate opioid analgesia: mu, delta, and kappa. Activation of the mu-opioid receptor produces both analgesic and euphoric effects. Mu-opioid receptors are found within the CNS, the gastrointestinal (GI) tract, and peripherally in areas and tracts associated with pain perception, sensory nerves, and mast cells.^{69,70} Mu-opioid activation is highly variable and interpatient responses therefore vary. Factors such as renal and hepatic function, age, and genetic factors also affect an individual's response to opioids.^{71,72}

Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists. Full agonists' effectiveness increases with increasing doses and is not limited by a ceiling. Full agonists will not reverse or antagonize the effects of other full agonists given simultaneously. Morphine, hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, methadone, levorphanol, fentanyl, and heroin are classified as full agonists.⁷³ Partial agonists (such as buprenorphine) are subject to a ceiling effect and are less effective analgesics than full agonists at mu-opioid receptors.⁷³ Opioid antagonists such as naltrexone and naloxone antagonize the effect of opioids and will precipitate a withdrawal syndrome.^{3,73}

Buprenorphine has poor oral bioavailability, which is improved by sublingual or buccal administration. Both sublingual and buccal buprenorphine formulations were developed for the treatment of opioid dependence. When administered via the sublingual and buccal routes, buprenorphine therapy is associated with a lower risk of abuse, as the rate at which it enters the bloodstream is significantly reduced compared to parenteral administration.⁵⁰ The addition of naloxone further reduces the risk of diversion and abuse. Naloxone is associated with poor bioavailability when given via the sublingual route with good bioavailability when given via the nasal or parenteral route. Sublingual use results in little to no mu-opioid effect. Other routes of administration may result in opioid withdrawal symptoms.⁷⁴ A limited number of pharmacokinetic studies are available comparing the bioavailability and tolerability of the buprenorphine/naloxone combination agents (sublingual tablets, sublingual films, buccal film). These have found some differences in the pharmacokinetic parameters. Systemic exposures are noted when comparing buprenorphine/naloxone sublingual tablets and sublingual films. Bioavailability may differ between formulations requiring different dosage strengths. For instance, BUP/NX RD SL tablet 5.7/1.4 mg, generic BUP/NX SL tablet 8/2 mg and BUP/NX buccal film 4.2/0.7 mg have similar bioavailability as BUP/NX SL film 8/2 mg. BUP/NX RD SL tablet 5.7/1.4 mg and BUP/NX SL film 8/2 mg may dissolve faster than generic BUP/NX SL tablet 8/2 mg.^{19,75,76} The risk of under- or overdosing may occur and patients should be monitored for potential dosage adjustments.¹⁹

The onset of action is 30 to 100 minutes for oral formulations (BUP SL, BUP/NX SL, and NTX tablets). Buprenorphine implant achieves its peak effect 12 hours following insertion. The depot formulation of XR-NTX gradually releases medication from polymer microspheres⁷⁷ Upon administration, the biphasic release system produces plasma drug-concentration peaks approximately 2 hours after injection and again in 2 to 3 days.²¹

Buprenorphine and naltrexone products are primarily metabolized by the liver. Metabolism of buprenorphine produces the metabolite norbuprenorphine, with unknown opioid activity.¹⁹ Naltrexone is metabolized through dihydrodiol dehydrogenase to produce the primary metabolite, 6 β -naltrexol, exhibiting some antagonist activity. Buprenorphine is a substrate of hepatic microsomal enzyme CYP3A4. Caution is required when buprenorphine products are administered with CYP3A4 inhibitors (e.g. azole antifungal agents, macrolide antibiotics, or HIV protease inhibitors) or inducers.^{15,19} Buprenorphine also acts as an inhibitor of CYP2D6 and CYP3A4.^{15,19} Naltrexone metabolism is unaffected by hepatic cytochromal enzymes.

Buprenorphine's elimination half-life ranges from 24 to 42 hours when buprenorphine is combined with naloxone and administered as a sublingual film, and 37 hours with buprenorphine sublingual tablet monotherapy. The elimination half-life of naltrexone and its metabolite (6 β -naltrexol) is five to ten days.

Buprenorphine is primarily excreted in the feces. Excretion of naltrexone occurs through the urine, primarily as metabolites (percentages not reported in the product labeling). The therapeutic duration of action for XR-NTX is approximately one month consistent with the labeled dosing interval. Buprenorphine implants are replaced every 6 months.

Table 5. Pharmacokinetics of Opioid Use Disorder Treatment Agents^{15-23,27}

Agents	Bioavailability	Time to peak	Protein binding	Metabolism	Excretion	Elimination Half-life
Buprenorphine	- Sublingual tablet: 29% <u>Effects of food:</u> Exposure reduced with liquids	- Sublingual: 30 minutes to 1 hour - Subdermal implant: 12 hours after insertion, with steady state achieved by week 4	96% (primarily to alpha- and beta globulin)	Liver: extensive Active metabolite: norbuprenorphine Substrate of CYP3A4, CYP2D6 and CYP3A4 inhibitor	Feces (~70%); urine (27% to 30%)	- Sublingual tablet: ~37 hours (may be due to depot effect [Kuhlman 1996])
Buprenorphine/naloxone*	- Sublingual tablet: 15% (buprenorphine); 3% (naloxone) <u>Effects of food:</u> Exposure reduced with liquids	- Sublingual film: 1.53 to 1.72 hours (buprenorphine); 0.77 to 0.81 hours (naloxone)	<u>Buprenorphine:</u> 96% <u>Naloxone:</u> 45%	<u>Buprenorphine:</u> Liver: extensive Active metabolite: norbuprenorphine Substrate of CYP3A4 CYP2D6 and CYP3A4 inhibitor <u>Naloxone:</u> Liver: extensive (primary site via glucuronidation, N-dealkylation, and reduction of the 6-oxo group)	<u>Buprenorphine:</u> Feces (~70%); urine (27% to 30%) <u>Naloxone:</u> Renal: 25% to 40% as metabolites (within 6 hours), about 50% (in 24 hours), 60% to 70% (in 72 hours)	- Sublingual film, used sublingually or buccally: 24 to 42 hours (buprenorphine); 2 to 12 hours (naloxone)
Naltrexone	<u>Oral:</u> Variable range (5% to 40%)	- <u>Oral:</u> ~60 minutes - <u>IM:</u> Biphasic: ~2 hours (first peak), ~2-3 days (second peak)	21%	<u>IM:</u> Liver: extensive (significant via dihydrodiol dehydrogenase and conjugation; extra-hepatic) <u>Oral:</u> Extensive first-pass effect Active metabolite: 6-beta-naltrexol	Renal: 53% to 79% (also as metabolites), less than 2% unchanged	- 5 to 10 days (dependent on erosion of the polymer) - 6-beta-naltrexol: 5 to 10 days

Abbreviations: IM, intramuscular;

* The exposure of one buprenorphine 4.2 mg/naloxone 0.7 mg buccal film is equivalent to one buprenorphine 8 mg/naloxone 2 mg sublingual tablet

Special Populations

Several patient populations require special consideration when treated with opioid dependence treatment agents: pediatric patients, geriatric patients, patients with liver or renal impairment, pregnant women, and patients with human immunodeficiency virus infection (HIV) or acquired immune deficiency syndrome (AIDS).

Pediatric Patients

The safety and efficacy of the buprenorphine combination products are not established in children under the age of 16. Some evidence suggests that pediatric patients (aged 15-21) with advanced illnesses (injection drug use and additional health problems) respond well to buprenorphine/naloxone therapy in community-based settings.⁷⁸ A second study evaluating the cost-effectiveness of extended buprenorphine treatment compared to brief detoxification found outpatient treatment with buprenorphine in opioid-dependent youth is cost-effective in the US health-care system.^{79,80} Case reports document accidental exposures to buprenorphine/naloxone in children, resulting in fatal overdoses.⁸¹ Buprenorphine products should be stored out of reach of children. Of note, prolonged use of buprenorphine during pregnancy may result in neonatal opioid withdrawal syndrome, which can be life-threatening if not detected.^{82,83}

Naltrexone products are not indicated in the pediatric population under 18 years old, since the safety and efficacy have not been established.^{21,22}

Geriatric Patients

No well-designed studies have evaluated opioid dependence therapy in the geriatric population with buprenorphine or naltrexone products.^{15,19,21,22} Criteria for selecting an agent in the elderly includes: side-effect profile, duration of action, drug interactions, and practical issues, such as cost and availability of the drug.⁸⁴ Buprenorphine does not demonstrate an increased half-life in patients with renal dysfunction; but, because it is excreted by the kidneys, cautious dosing is recommended to reduce the risk of adverse events.⁸⁴

Renal Impairment

Buprenorphine has not been studied in patients with renal impairment. Dosage adjustments are not recommended but buprenorphine products should be used with caution.^{15,17} Naltrexone does not require dose adjustment for mild renal impairment (creatinine clearance 50-80 mL/min); however, caution should be exercised in patients with moderate to severe renal impairment since no pharmacokinetic studies have been performed.^{21,22}

Liver Impairment

All opioid agents are metabolized by the liver and should be used with caution in patients with hepatic disease.²³ Bioavailability is increased after oral administration and additive effects may result from reduced metabolism or elimination in this patient population. For instance, the dose of buprenorphine monotherapy requires a 50% reduction in patients with severe hepatic impairment.¹⁵ Buprenorphine/naloxone combination products should not be administered in patients with severe hepatic impairment and should be used with caution in patients with moderate hepatic impairment.^{70,82,85} Naltrexone dose adjustments are not required for mild to moderate hepatic impairment (Group A and B, Child-Pugh classification) and caution should be exercised in patients with severe liver impairment since no pharmacokinetic studies have been performed.^{21,22}

Patients with HIV/AIDS

Unsafe injection practices, particularly that of opioids, continue to fuel the global epidemic of human immunodeficiency virus infection (HIV) and acquired immune deficiency syndrome (AIDS).⁶⁶ A successful strategy to prevent the transmission of HIV must include a plan to reduce the rate of unsafe opioid injecting and effectively treat opioid dependence. Patients with HIV/AIDS who require opioid dependence treatment may benefit from buprenorphine therapy. One study found that opioid dependence treatment outcomes in patients with HIV were sustained in those receiving buprenorphine combination therapy and improved in patients at highest risk for clinical deterioration.⁸⁶ Drug interactions with buprenorphine and protease inhibitors report concurrent administration is safe and dose adjustments are usually not required.⁸⁷

Pregnancy and lactation

Monotherapy with the opioid agonists, methadone and buprenorphine, is preferred in pregnant women with physical dependence because the benefits to the mother and fetus outweigh the risks. Insufficient data are available for buprenorphine/naloxone combination products and they are not recommended during pregnancy. Both psychological support and pharmacological treatment is encouraged.⁶

Breastfeeding is encouraged in pregnant women on treatment with methadone or buprenorphine monotherapy to minimize withdrawal in the neonate. Breastfeeding is not recommended during naltrexone therapy.⁶

Table 6. Recommendations for Special Populations of Opioid Use Disorder Treatment Agents^{15-23,27}

Agents	Renal Impairment	Hepatic Impairment	Pregnancy and lactation	Pediatric	Geriatric
Buprenorphine sublingual tablet	No dosage adjustments. Use with caution.	Mild impairment (Child-Pugh class A): No dosage adjustment necessary. Moderate impairment (Child-Pugh class B): No dosage adjustment necessary; use caution Severe hepatic impairment: Reduce the starting and incremental dose by 50%	Pregnancy: <ul style="list-style-type: none"> <i>Pregnancy Category C:</i> There are no adequate studies assessing buprenorphine use in pregnant patients Adverse effects have been observed in some animal reproduction studies at higher doses. Methadone or buprenorphine monotherapy should be used in pregnant women with OUD Life-threatening neonatal opioid withdrawal syndrome may appear with the long-term use of opioids Lactation: <ul style="list-style-type: none"> Buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. 	The safety and efficacy of buprenorphine have not been established in pediatric patients <16 years	Caution in elderly or debilitated patients
Buprenorphine implant	No dosage adjustments, has not been studied. Use with caution	Mild impairment: no dosage adjustment. Not studied Moderate or severe impairment: Use is not recommended	Pregnancy <ul style="list-style-type: none"> <i>Pregnancy Category C:</i> There are no adequate studies assessing buprenorphine use in pregnant patients Adverse effects have been observed in some animal reproduction studies at higher doses. Methadone or buprenorphine monotherapy should be used in pregnant women with OUD Life-threatening neonatal opioid withdrawal syndrome may appear with the long-term use of opioids Lactation: Buprenorphine passes into the mother's milk. Available data have not shown adverse reactions in breastfed infants.	The safety and efficacy of buprenorphine have not been established in pediatric patients <16 years	Not studied. Use with caution. Monitor elderly patients for sedation or respiratory depression

Buprenorphine/ naloxone	No dosage adjustments. Not studied. Use with caution	Mild impairment: no dosage adjustment. Moderate impairment: Use with caution Severe impairment: Use is not recommended	Pregnancy: <ul style="list-style-type: none"> Buprenorphine/naloxone combination product is not recommended because there is insufficient data available Life-threatening neonatal opioid withdrawal syndrome may appear with the long-term use of opioids Lactation: There are no data on the combination product buprenorphine/naloxone in breastfeeding. Buprenorphine passes into the mother's milk and oral absorption of naloxone is minimal	The safety and efficacy of buprenorphine have not been established in pediatric patients <16 years	See adult dosing
Naltrexone (oral or injectable)	No dose adjustment is necessary for mild renal insufficiency (CrCl 50-80 mL/min); use with caution in moderate to severe renal impairment since pharmacokinetic studies have not been conducted to guide therapy decisions	Dose adjustment is not necessary for mild to moderate hepatic. Impairment. Severe impairment: The pharmacokinetics were not evaluated in patients with severe hepatic impairment. Naltrexone AUC increased ~5- and 10-fold in patients with compensated or decompensated hepatic cirrhosis respectively	Pregnancy: There are no adequate RCTs assessing naltrexone use in pregnant patients. Naltrexone should only be used if the potential benefit justifies the potential risk to the fetus. <ul style="list-style-type: none"> Pregnancy Category C: Naltrexone has been shown to increase the incidence of early fetal loss when given to rats at doses ≥ 30 mg/kg/day (11 times the human exposure based on an AUC (0-28d) comparison) and to rabbits at oral doses ≥ 60 mg/kg/day (2 times the human exposure based on an AUC (0-28d) comparison). No evidence of teratogenicity was found in rats or rabbits when naltrexone was administered at doses up to 200 mg/kg/day (175- and 14-times the human exposure based on AUC, respectively). Lactation: Transfer of naltrexone and its active metabolite into human breast milk has been reported. The potential risk for tumorigenicity (shown for naltrexone in animal studies) and risk of adverse reactions in the nursing infant and mother should be weighed against the benefits of therapy.	The safety, efficacy, and pharmacokinetics have not been established for this population	See adult dosing. No patients >65 were included in the studies leading to the approval of Vivitrol for OUD management.

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; OUD, opioid use disorder; RCTs, randomized controlled trials

Methods

Literature Search

Search strategies were developed by an informational scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. Two methodological filters were used, one for systematic reviews and another for randomized controlled trials (RCTs). Results were limited to English language. Databases were searched from date of inception forward. In EMBASE, we excluded conference abstracts. Searches were conducted in August 2017. The complete search strategies and terms are available in **Appendix A**.

We also screened the reference lists of related systematic reviews. Likewise, we searched other relevant websites for further information:

1. The American Society of Addiction Medicine (ASAM), the Centers for Disease and Control (CDC) and the World Health Organization (WHO) websites for the most recent treatment guidelines
2. U.S. Department of Health and Human Services, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Utah Department of Health websites for general information
3. Food and Drug Administration (Drugs@FDA: FDA Approved Drug Products: <https://www.accessdata.fda.gov/scripts/cder/daf/>) for prescribing information package inserts
4. Evidence-based drug information databases (Micromedex, Lexicomp, and UpToDate)

Screening

At least two review authors screened titles and abstracts. The full texts for all citations receiving two inclusion votes were retrieved; eligibility criteria for inclusion were determined by the lead author. Conflicts were resolved via discussion between reviewers or a third person. Figure 1 shows the PRISMA flow chart⁸⁸ for the review process.

Inclusion and Exclusion Criteria

Systematic reviews and RCTs providing head-to-head efficacy comparisons between the agents for OUD described in **Table 1** were included. For product comparisons where a systematic review provided robust data, we examined only those trials or systematic reviews published after the search date of the robust systematic reviews. A list containing the excluded references is provided in **Appendix E**.

Excluded references met the following exclusion criteria:

- Studies evaluating non-FDA-approved doses or indications (e.g. drug withdrawal) and studies evaluating alcohol dependence only
- Studies comparing methadone with other agents for OUDs
- Other types of studies (e.g. non-comparative or non-randomized trials, placebo-controlled studies, phase 1 and 2 studies, observational studies, in vitro studies, animal studies, cost-effectiveness studies, etc.)
- Reviews not using systematic review methodology

In addition to the search strategies performed, relevant information from the following Drug Class Reviews prepared by the University of Utah's Drug Regimen Review Center was incorporated into this report:

1. Opioid Dependence Treatment with Vivitrol, extended-release naltrexone (April 2017)
2. Opioid Dependence Treatment with Buprenorphine (November 2016)
3. Opioid Dependence Treatment Agents, buprenorphine & naloxone (January 2015)

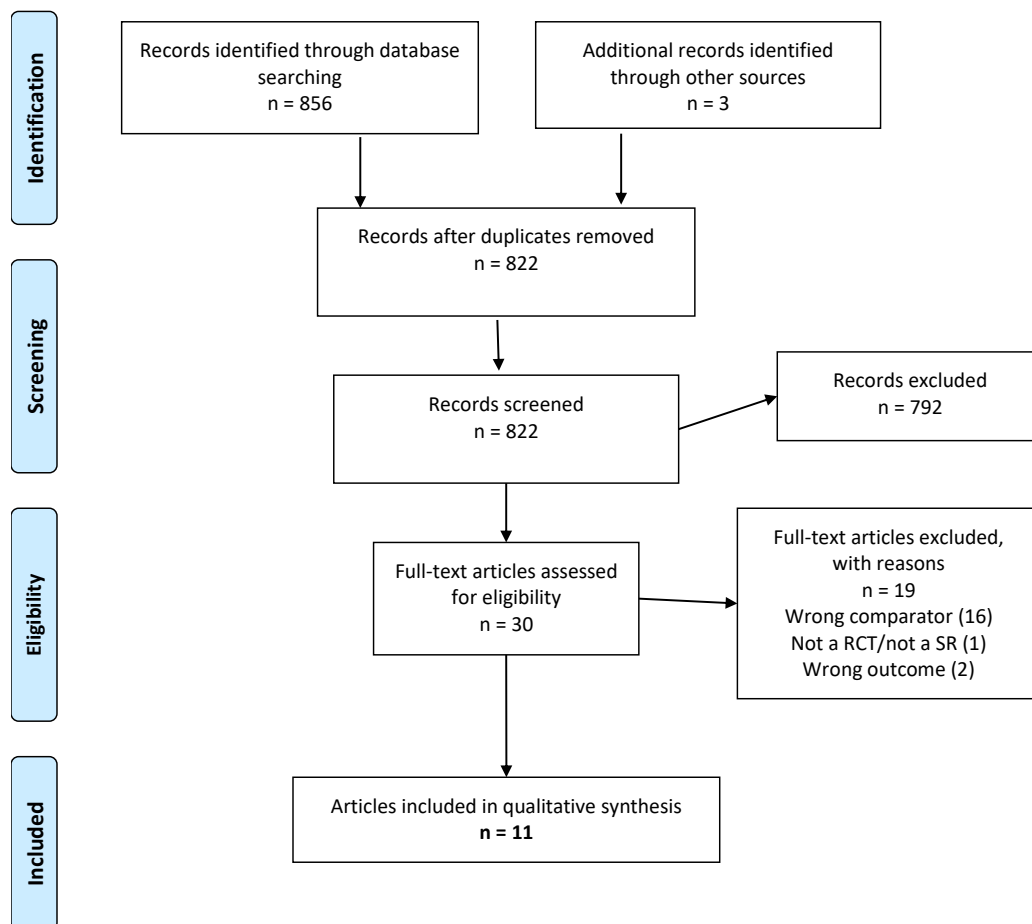


Figure 1. PRISMA Flow Diagram of the selection process

Clinical Efficacy and Safety

Clinical evidence involving head-to-head comparisons among the FDA-approved agents for the treatment of OUD (excluding methadone) is presented in this report.

Two relevant clinical guidelines published in 2015 (outlined in **Table 3**) were identified: the *ASAM National practice guidelines for the use of medications in the treatment of addiction involving opioid use* and the *Veteran Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for the Management of Substance Use Disorders*. These two documents included clinical recommendations based on systematic reviews of the literature found through April 2014 for the ASAM guideline⁶ and January 2015 for the VA/DoD guideline.⁶⁰ A systematic literature search for RCTs was performed only for the time period of January 2015 to July 2017. From 822 references identified using the developed search strategy, 11 references were included in the report (3 Cochrane systematic reviews, 2 systematic reviews informing the two most recent guidelines and 6 articles including 5 RCTs).

Summary of evidence tables can be found in **Appendixes B, C and D**.

Buprenorphine/naloxone versus other buprenorphine/naloxone formulations or oral buprenorphine monotherapy

Cochrane reviews (2 reviews from Minozzi 2014^{89,90})

The comparative clinical evidence evaluating the buprenorphine products is limited. **Minozzi et al (2014)** conducted two Cochrane systematic reviews^{89,90} evaluating two randomized controlled trials (RCT), one of interest for this report (Woody et al 2008⁸⁰). Both Cochrane reviews assessed buprenorphine (up to 24 mg/day)/naloxone (0.5 mg) for maintenance therapy during 9 weeks (then tapered to week 12) versus buprenorphine (up to 14 mg/day) for detoxification therapy during 14 days in adolescents with OUD. Patients were followed-up over one year and counselling was offered.

- Results from both reviews reported a lower number of drop-outs at week 12 and reduced self-reported heroin use after 12 months in the maintenance group with buprenorphine/naloxone than detoxification group with buprenorphine. These results were statistically significant.
- No differences between groups were observed concerning the number of patients with opiate positive urine analysis at week 12 and the use of other substances such as alcohol and marijuana at month 12.
- The authors considered one study with 150 patients to provide limited evidence. No sound conclusions were drawn from these reviews.

Randomized controlled trials (2 RCTs, 3 articles: Webster 2016⁹¹, Gunderson 2015⁹² and Gunderson 2016⁹³)

Two RCTs^{91,92} assessing the efficacy and safety of buprenorphine monotherapy versus buprenorphine/naloxone were identified. One RCT^{92,93} also evaluated two different buprenorphine/naloxone formulations (BUP/NX RD SL tablet versus BUP/NX SL film).

- **Webster et al⁹¹ (2016)** conducted a non-inferiority trial comparing BUP/NX RD SL tablet with generic BUP SL tablet alone for induction therapy in 313 opioid dependent adults.
 - The study was unable to demonstrate non-inferiority of BUP/NX RD SL tablet versus generic BUP SL tablet in terms of treatment retention at day 3. More patients were retained in the BUP group than in BUP/NX group (122/128 patients; 95.3% and 113/128 patients; 88.3%, respectively; 95% CI: **-13.7**, -0.4; $p=0.040$; non-inferiority was shown if lower limit of the 95% CI $\geq -10\%$). However, this study had several limitation such as different baseline physical dependence or disease severity between groups, and higher number of discontinuations and withdrawals in the group receiving BUP/NX RD SL tablets.
 - The authors performed a pooled analysis combining the treatment retention results from this trial with the results of the study conducted by Gunderson et al⁹² (2015). A total of 1,068 patients were included in the pooled analysis. Similar treatment retention rates between groups were reported at day 3 (91% with BUP/NX vs 92.6% with BUP, 95% CI: -5.0, 1.5 $p=0.30$). No formal non-inferiority limit was established.
 - The authors cited a different study⁹² (mentioned below) including 758 patients. This trial reported a similar treatment retention rate at day 3 (induction phase) between BUP alone and BUP/NX RD SL tablet.
 - Secondary endpoints such as clinical withdrawal symptoms, craving and safety profiles were similar between both groups.
- **Gunderson et al⁹² (2015)** performed a non-inferiority trial in 758 opioid dependent adults during induction and stabilization phases. In the induction phase (day 1 to day 3) patients received blinded BUP/NX RD SL tablet or generic buprenorphine. The stabilization phase (day 3 to day 14) was open-labeled and compared BUP/NX RD SL tablet versus BUP/NX SL film.
 - Non-inferiority for the co-primary endpoint of treatment retention was demonstrated between BUP/NX RD SL tablet and generic buprenorphine during the induction therapy at day 3.
 - Non-inferiority was demonstrated regarding treatment retention rate between BUP/NX RD SL tablet and BUP/NX SL film during the stabilization phase at day 15.
 - Safety profiles were comparable between buprenorphine alone and the two formulations of buprenorphine and naloxone.

- **Gunderson et al⁹³ (2016)** reported the results of the above non-inferiority study⁹² from day 15 to day 22 (switching phase). During this phase, patients switched from BUP/NX RD SL tablet to BUP/NX SL film and vice-versa.
 - Both switching groups reported comparable treatment retention rates (more than 90% in both groups), and similar opioid withdrawals and craving symptoms.
 - Preference ratings at day 22 favored BUP/NX RD SL tablet for taste, mouth-feel, ease of administration and overall preference ($p < 0.0001$)
 - Safety profiles were similar between treatment groups

Buprenorphine implant versus buprenorphine sublingual tablet

Randomized controlled trials (1 RCT: Rosenthal 2016⁹⁴)

- **Rosenthal et al⁹⁴ (2016)** conducted a non-inferiority trial of BUP implants compared to BUP SL for maintenance therapy in opioid dependent patients. A total of 177 adult patients stable for 90 days were randomized to one of the treatment groups.
 - Regarding the primary endpoint of the proportion of participants with no illicit opioid use during at least 4 of 6 months of treatment, BUP implants were non-inferior to BUP SL tablets.
 - Secondary endpoints indicated a significantly higher number of abstinent patients and longer time to first use of an illicit opioid use in BUP implant group compared to BUP SL tablet group.
 - Several limitations were detected. The study was under-powered to identify differences in adverse events and the characteristics of the population were not representative of the usual population requiring these types of medications. This may have led to the high rate of responders in the BUP SL tablet group. Authors concluded that further research is needed in larger populations to evaluate the efficacy and safety of BUP implants versus BUP SL tablets.

Oral naltrexone versus buprenorphine or buprenorphine/naloxone

Cochrane reviews (1 review: Minozzi 2011⁹⁵)

Minozzi et al⁹⁵ (2011) performed a Cochrane systematic review evaluating the effects of oral naltrexone for the maintenance treatment of OUDs, after detoxification therapy. Among the thirteen studies included in the review, one single study compared naltrexone plus psychosocial therapy versus buprenorphine plus psychosocial therapy (Schottenfield 2008⁹⁶).

- Main results indicated no differences between NTX tablets and buprenorphine for the outcomes of retention and abstinence, with a trend to favor buprenorphine (Relative risk 0.37; 95% CI 0.13-1.08).

- However, authors concluded that the available studies preclude a proper evaluation of oral naltrexone in the treatment of opioid dependence.

Randomized controlled trials (2 RCTs: Mokri 2016⁹⁷, Ahmadi 2003⁹⁸)

- One RCT conducted in Iran by **Mokri et al**⁹⁷ evaluated the efficacy of oral naltrexone versus BUP/NX SL tablets. This study included 102 participants with OUD (opium or heroin dependence) and lasted for 12 weeks (follow-up through week 24). All participants were enrolled in a medically assisted detoxification program before starting the trial and received drug counselling.
 - The results from the primary endpoint (i.e. mean number of days of opioid abstinence confirmed by urine tests) and from one of the secondary endpoints (i.e. proportion of subjects with opioid-abstinence for 12 weeks) were similar between both groups ($p=0.205$ and $p=0.219$, respectively).
 - The other two secondary endpoints showed a higher number of opioid negative urine tests (19.7 vs. 15.4 number of negative tests; $p=0.049$) and increased treatment retention in the BUP/NX group compared to oral naltrexone group (70.6 vs 56.5 days of retention; $p=0.013$). Similar treatment retention tendency was observed from week 12 to week 24.
 - Results from other aforementioned studies (Schottenfield 2008⁹⁶ performed in Malaysia and Minozzi 2011,⁹⁵ a Cochrane review including Schottenfield 2008) showed a higher treatment retention rate with buprenorphine alone compared to oral naltrexone in heroin dependent patients. Several studies have associated poor treatment retention with an increased risk of drug overdose, relapse and HIV transmission.
 - Better treatment adherence is expected with the XR-NTX. However, no head-to-head studies comparing XR-NTX versus buprenorphine or oral naltrexone are available.
- **Ahmadi et al**⁹⁸ (2003) performed a 24-week RCT evaluating methadone 50 mg, buprenorphine SL tablet 5 mg/day and 50 mg oral naltrexone in patients with intravenous-buprenorphine dependence. Treatment retention in the 5-mg oral buprenorphine group was significantly better than in the 50-mg naltrexone dose group ($p= 0.000$).

Findings from ASAM and VA/DoD guidelines

Authors developing the ASAM and VA/DoD guidelines performed systematic reviews searching up to April 2014 and January 2015, respectively. In relation to head-to head comparisons between buprenorphine, buprenorphine/naloxone, naltrexone injectable and naltrexone oral tablets, findings from the systematic review conducted by ASAM identified a lack of comparative studies in the treatment of OUD. The need for further research in this area is highlighted. Alternatively, VA/DoD guideline establishes buprenorphine/naloxone and methadone as first line options based on high quality evidence from RCTs and meta-analyses. Extended-release naltrexone is recommended as a second line treatment for OUD based on one

RCT.⁷⁷ With regards to oral naltrexone, VA/DoD guideline mentioned one RCT (Schottenfeld 2008⁹⁶) showing better performance of oral buprenorphine versus oral naltrexone in terms of time to first heroin use, time to heroin relapse and retention.

No direct comparisons evaluating XR-NTX versus other agents for OUD are available. The literature search identified two clinical trials comparing XR-NTX versus buprenorphine/naloxone; however, results have not yet been published:

1. *Naltrexone vs. Buprenorphine-Naloxone for Opioid Dependence in Norway (NTX-SBX)*.⁹⁹ Current status in clinicaltrials.gov: study ongoing, but not recruiting participants.
2. *Extended-Release Naltrexone vs. Buprenorphine for Opioid Treatment*.¹⁰⁰ Current status in clinicaltrials.gov: study completed, results unpublished.

Safety

In general, the most common adverse events reported with opioid agents include headache, nausea, vomiting, sedation, pruritus, and constipation.^{82,85} Serious adverse events that are frequently reported with opioid use include respiratory depression, urinary retention, hypotension, and delirium. Buprenorphine oral formulations, in particular, are associated with limited respiratory depression and a ceiling effect at higher doses, unlike fentanyl and many of the other opioid analgesics.¹⁰¹ There are case reports of overdose fatalities with buprenorphine use in pediatric patients or when it is used in combination with benzodiazepines, especially when administered parenterally.¹⁰² Risk factors for increased rates of opioid-related serious adverse effects include differences in potency between the agents, prescribing by multiple prescribers or filling at multiple pharmacies, complicated medication regimens, and lack of education and communication between providers and patients.^{69,70}

Methadone and buprenorphine are associated with abuse at much lower rates than oxycodone or morphine.³³ It has been reported that, when addicts injected intravenously, they claim buprenorphine produces effects similar to equipotent doses of morphine or heroin.¹⁰³ The buprenorphine/naloxone combination products are efficacious in reducing the risk of diversion and abuse because naloxone produces an antagonist effect when crushed and used via the nasal or intravenous route. Naltrexone does not induce opioid-related physical dependence and withdrawal symptoms when treatment is discontinued, and the risk of diversion is low compared to that of methadone and buprenorphine containing products.³⁰

The buprenorphine implant can migrate, causing embolism and death. The insertion and extraction procedure may also result in nerve damage. These serious and life-threatening adverse effects together with a reference to the Probuphine Risk Evaluation and Mitigation Strategies (REMS) program are included as a black box warning in the package insert.¹⁶

Both naltrexone formulations are well tolerated. The most common adverse events described in trials with XR-NTX include injection site pain, hepatic enzyme abnormalities, nasopharyngitis, insomnia, and toothache, occurring at rates of 2% or more and at least twice as frequently as in the placebo group.²¹ Adverse events of oral naltrexone occurring with an incidence of 10% or higher in clinical trials include sleeping difficulties, anxiety, nervousness, abdominal pain and cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.²² One of the main warnings for naltrexone is the requirement for an opioid-free period of 7 to 10 days prior to initiating naltrexone in order to avoid withdrawal syndrome and potential hospitalization.²¹ Buprenorphine products are also indicated for the maintenance therapy of OUD, but do not require a long period without opioid drug administration.¹¹ Proper usage and risks involved with XR-NTX therapy are emphasized through the FDA's Risk Evaluation Mitigation Strategy (REMS) program.¹⁰⁴ Patient counseling tools and an injection technique

guide are education materials available to healthcare providers through this program. Poor adherence to oral naltrexone has been reported in several studies,^{95,96} which may be improved with the use of XR-NTX.

Table 7 contains information about warnings and adverse events related to OUD treatment agents.

Table 7. Warnings and Adverse Events of Opioid Use Disorder Treatment Agents^{15-23,27}

Agents	Warnings and Precautions	Adverse Events
Buprenorphine Sublingual tablet	<ul style="list-style-type: none"> • Risk of abuse, addiction, misuse. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits • Respiratory depression and death, especially with the concurrent use of BUP IV and BZPs/alcohol/CNS depressants • Accidental exposure: BUP can cause severe, possibly fatal, respiratory depression in children • Hypersensitivity to active substances 	<p>>10%:</p> <ul style="list-style-type: none"> • Central nervous system: Headache (29%), insomnia (21%) • Dermatologic: Diaphoresis (13%) • Gastrointestinal: Nausea (14%), abdominal pain (12%), constipation (8%) • Infection: Infection (12%) <p>1% to 10%:</p> <ul style="list-style-type: none"> • Gastrointestinal: Vomiting (8%)
Buprenorphine/naloxone	<ul style="list-style-type: none"> • Physical dependence; withdrawal upon abrupt discontinuation • Liver insufficiency. Not recommended in severe hepatic impairment • Neonatal withdrawal syndrome possible with perinatal use • Adrenal Insufficiency • Not appropriate as an analgesic • Drug-drug interactions involving CYP-enzymes • Anti-retrovirals: Some potential interactions, but appear to be fewer interactions vs methadone possibly due to different route of absorption (sublingual or buccal); less competitive.^{46,105} 	<p>>10%:</p> <ul style="list-style-type: none"> • Central nervous system: Headache (36%), withdrawal syndrome (25%; placebo 37%), pain (22%) • Dermatologic: Diaphoresis (14%) • Gastrointestinal: Glossodynia (film), oral hypoesthesia (film), oral mucosa erythema (film) <p>1% to 10%:</p> <ul style="list-style-type: none"> • Cardiovascular: Vasodilatation (9%) • Gastrointestinal: Vomiting (8%)
Buprenorphine Implant	<p><u>Black box warning:</u></p> <ul style="list-style-type: none"> • IMPLANT MIGRATION, PROTRUSION, EXPULSION, and NERVE DAMAGE ASSOCIATED WITH INSERTION and REMOVAL • PROBUPHINE is available only through a restricted program called the PROBUPHINE REMS Program <p>See also buprenorphine sublingual tablet applicable precautions</p>	<p>>10%:</p> <ul style="list-style-type: none"> • Central nervous system: Headache (13%) • Dermatologic: Pruritus (12%; at implant site) • Miscellaneous: Pain at medication pump site (4% to 13%) <p>1% to 10%:</p> <ul style="list-style-type: none"> • Cardiovascular: Edema (5%; at implant site), chest pain (1%) • Central nervous system: Depression (6%), dizziness (4%), drowsiness (3%), fatigue (3%), chills (2%), migraine (2%), paresthesia (1%), sedation (1%), sensation of cold (1%) • Dermatologic: Erythema (10%; at implant site), skin rash (2%), excoriation (1% to 2%; including scratch), skin lesion (1%) • Gastrointestinal: Constipation (6%), nausea (6%), vomiting (6%), toothache (5%), upper abdominal pain (3%), flatulence (1%) • Hematologic & oncologic: Hemorrhage (7%; at implant site) • Local: Local swelling (1%)

		<ul style="list-style-type: none"> • Neuromuscular & skeletal: Back pain (6%), limb pain (3%), weakness (2%) • Respiratory: Oropharyngeal pain (5%), cough (3%), dyspnea (1%) • Miscellaneous: Fever (3%), laceration (3%)
Naltrexone (Oral and Injection)	<ul style="list-style-type: none"> • Precipitated withdrawal if given before opioid free washout period; may be severe enough to require hospitalization (opioid-free period of 7-10 days is recommended; • Abstinence from opioids can be difficult for patients to achieve • Vulnerability to opioid overdose • Injection site reactions/hypersensitivity • Hepatotoxicity • Depression and Suicidality: monitor patients • Pain management challenges 	<p>Adverse events for naltrexone (oral and injectable)</p> <p>>10%:</p> <ul style="list-style-type: none"> • Cardiovascular: Syncope (13%) • Central nervous system: Headache (3% to 25%), insomnia (3% to 14%), dizziness (4% to 13%), anxiety (2% to 12%), decreased energy (>10%), nervousness (4% to >10%) • Gastrointestinal: Nausea (10% to 33%), vomiting (3% to 14%), decreased appetite (14%), diarrhea (13%), abdominal pain (11%), abdominal cramps • Hepatic: Increased serum ALT (13%) • Local: Injection site reaction (≤69%; includes bruise, induration, nodules, pain, pruritus, swelling, tenderness) • Neuromuscular & skeletal: Increased creatine phosphokinase (11% to 39%), arthralgia (12%), myalgia (>10%) • Respiratory: Pharyngitis (7% to 11%) <p>1% to 10%:</p> <ul style="list-style-type: none"> • Cardiovascular: Hypertension (5%) • Central nervous system: Suicidal ideation (≤10%), delayed ejaculation (<10%), depression (8%), drowsiness (2% to 4%), fatigue (4%), chills, depressed mood, increased energy, irritability • Dermatologic: Skin rash (6% to 10%) • Endocrine & metabolic: Increased gamma-glutamyl transferase (7%), increased thirst, polydipsia • Gastrointestinal: Xerostomia (5%), toothache (4%), constipation • Genitourinary: Impotence (<10%) • Hepatic: Increased serum AST (2% to 10%) • Infection: Influenza (5%) • Neuromuscular & skeletal: Muscle cramps (8%), back pain (6%)

Abbreviations: AE, adverse effects; BUP, buprenorphine; BZPs, benzodiazepines; CNS, central nervous system; CYP, cytochrome P450; IV, intravenous; NTX, naltrexone; OTP, opioid therapy programs; OUD, opioid use disorder; RCT, randomized controlled trial

Risk Evaluation and Mitigation Strategy (REMS) Programs

REMS programs are focused on managing and mitigating known and potential serious risks associated with drug products. REMS programs are required for some agents by the FDA to guarantee that the benefit-risk balance is positive. Three REMS programs are available for buprenorphine-containing products (oral formulations), BUP implant and XR-NTX.

Table 7. Risk Evaluation and Mitigation Strategy Programs

Agents	REMS Program		
	REMS Objectives	Patient Counseling Tool	Important Information for HCPs
Buprenorphine products (Oral)^{106*}	<ul style="list-style-type: none"> Mitigate the risks of accidental overdose, misuse, and abuse Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products 	<p>Patients should be informed about:</p> <ul style="list-style-type: none"> Risks of accidental overdose, misuse, and abuse Not to self-administer BZ or other CNS depressants while taking these drugs Keep out of the reach and sight of children Keep products in a safe place and protect them from theft Do not give to anyone else Selling or giving away is against the law 	<p>Certified prescribers should:</p> <ul style="list-style-type: none"> Verify that patients meet diagnostic criteria of OUD Counsel patients and caregivers on safe use Monitor and document safe use for each patient Assess appropriateness of treatment and adequate progress towards goals for each patient <p>Pharmacists should:</p> <ul style="list-style-type: none"> Verify prescription is from a prescribers in compliance to DATA 2000 Check quantity: limited supply during initial therapy Provide Medication guide to patients Patient counseling Detect fraudulent prescriptions or simultaneous prescriptions for the same patient
Buprenorphine implant¹⁰⁷	<ul style="list-style-type: none"> Mitigate the risk of insertion and removal complications Reduce the risk of accidental overdose, misuse and abuse REMS includes: <ul style="list-style-type: none"> Training Certification Recertification Patient counseling Closed distribution 	<p>Patients should be informed about:</p> <ul style="list-style-type: none"> The risks of insertion or removal of Probuphine The risks of accidental overdose, misuse, and abuse, if an implant comes out or protrudes from the skin The importance of appropriate wound care 	<ul style="list-style-type: none"> HCPs should be informed about the risks associated with insertion and removal: <ul style="list-style-type: none"> Migration Protrusion Expulsion Nerve damage HCPs should be informed about the risks associated with accidental overdose, misuse and abuse when Probuphine comes out the skin HCPs prescribing Probuphine must be trained and certified

			<ul style="list-style-type: none"> • HCPs inserting/removing Probuphine must be trained and certified • Distribution through a Closed Distribution System
Naltrexone IM injection¹⁰⁴	<ul style="list-style-type: none"> • Reduce risks • Inform prescribers, pharmacists, and patients of the serious risks associated with Vivitrol 	<ul style="list-style-type: none"> • Risk of opioid withdrawal during initiation and re-initiation of Vivitrol • Risk of overdose • Risk of severe injection site reactions • Risk of hepatotoxicity, including hepatitis • Patients may not feel the therapeutic effects of opioid-containing medicines for pain, cough or cold, or diarrhea while taking Vivitrol 	<p>Key techniques to reduce the risk of injection-site reactions:</p> <ul style="list-style-type: none"> • Proper needle selection • Proper aseptic technique • Proper Intramuscular (IM) injection

* Only applies to buprenorphine-containing oral transmucosal products not dispensed through OPT

Abbreviations: BZ, benzodiazepines; CNS, central nervous system; HCP, healthcare providers; IM, intramuscular; OTP, opioid treatment program; REMS, risk evaluation and mitigation strategy

Summary

Opioid use disorder is a chronic and relapsing disease that involves managing patients through the treatment induction or detoxification, and maintenance stages, with many patients needing long-term treatment. A paired pharmacological-psychosocial treatment approach has improved outcomes in both the detoxification and maintenance stages.

According to the guidelines, pharmacologic treatment options for the treatment of OUD include agonist therapy with methadone, partial agonist therapy with buprenorphine or antagonist therapy with naltrexone. The ASAM guideline does not currently recommend one product for OUD over another or provide a specific duration of treatment. The VA/DoD guideline classifies methadone and buprenorphine/naloxone combination therapy as first-line agents and extended-release naltrexone as a second-line option. No recommendations are provided for oral naltrexone in the management of OUD due to limited evidence available.

Five systematic reviews and five RCTs assessing direct head-to-head comparisons between the OUD agents included in this report were identified.

Two Cochrane reviews and two RCTs evaluated buprenorphine monotherapy versus buprenorphine/naloxone combination therapy. One RCT also compared buprenorphine/naloxone sublingual tablet with buprenorphine/naloxone sublingual film:

- The two Cochrane reviews included the same small study of interest. A lower incidence of drop-outs and reduced self-reported heroin use were reported in the buprenorphine/naloxone group (maintenance therapy) compared to buprenorphine alone group (detoxification therapy). Authors could not draw sound conclusions based on this single study.
- Two non-inferiority trials and one pooled analysis compared BUP/NX RD SL tablets versus generic buprenorphine alone for induction therapy. Results indicated similar treatment retention rates at day 3 (induction phase) between groups; although one of the studies with several limitations failed to demonstrate non-inferiority. One of these RCTs also evaluated buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone sublingual film from day 3 to day 14 (stabilization phase). Similar treatment retention rates were reported between groups.

One RCT assessed the efficacy of buprenorphine implant versus buprenorphine sublingual tablet for maintenance therapy. The study demonstrated non-inferiority between groups in terms of proportion of patients without illicit opioid use during at least 4 of 6 months of treatment. However, the study had several limitations and authors state further research is needed to confirm their results.

Oral naltrexone was compared to buprenorphine alone in one Cochrane review. Results showed no differences in treatment retention and abstinence between groups, with a trend to favor buprenorphine. One RCT evaluated the efficacy of oral naltrexone versus BUP/NX SL tablets indicating similar outcomes between groups for the primary endpoint of opioid

abstinence. For the secondary endpoint of treatment retention, a higher number of participants were retained in the buprenorphine/naloxone group compared to oral naltrexone group.

Naltrexone does not induce opioid-related habit forming effects; thus, the risk of diversion is low compared to that of methadone- and buprenorphine-containing products. Buprenorphine has abuse potential, but the addition of naloxone to buprenorphine reduces the risk of diversion and abuse because naloxone produces an antagonist effect when crushed and used via the nasal or intravenous route.

The main differences between products include the mechanism of action (partial agonist versus full antagonist), dosing (daily administration for oral buprenorphine and oral naltrexone products, monthly for extended-release naltrexone and every 6 months for buprenorphine implant), treatment setting (buprenorphine products require a special waiver for physicians and may be provided in an office-based setting or opioid treatment programs while naltrexone can be prescribed in any medical setting without restrictions), requirements for the induction phase (administration of buprenorphine products requires the presence of mild to moderate withdrawal symptoms, which precipitate 8 to 12 hours after last opioid while administration of naltrexone requires patients to be opioid-free for 7-10 days), treatment adherence (poor retention with oral naltrexone), and adverse events. Rates of diversion, physical dependence, and stigma are lower with naltrexone compared to buprenorphine products. The selection of an OUD treatment agent should be individualized and guided by the patient's disease history and personal preference in combination with the provider's assessment of the immediate and chronic effects of therapy and overall health status of the patient.

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102. Treatment. CfSA. Substance Abuse Treatment and Family Therapy. Treatment Improvement Protocol (TIP) Series. In. No. 39. *DHHS Publication No. (SMA) 05-4006*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
103. Clark H. Buprenorphine in the Treatment of Opioid Addiction: Balancing Medication Access with Quality Care. Opening Remarks February 21, 2008 from the Director of the Center for Substance Abuse Treatment (SAMHSA).
104. Vivitrol Risk Evaluation Mitigation Strategy: Information for Healthcare Providers. . <http://vivitrolrem.com/>.
105. Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep*. 2010;7(3):152-160.
106. Food and Drug Administration. Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD). Risk Evaluation and Mitigation Strategy (REMS). Revised May, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/rem/BTOD_2017-05-23_REMS_document.pdf.
107. Probuphine Risk Evaluation Mitigation Strategy: Information for Healthcare Providers. <https://probuphinerems.com/>.

Appendix A. MEDLINE and EMBASE Literature Search Strategies for Opioid Use Disorder Treatment Agents

MEDLINE SYSTEMATIC REVIEW STRATEGY [AUGUST 17, 2017]

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	
Search Strategy:	
1	buprenorphine, naloxone drug combination/ (200)
2	(buprenorphin* adj3 naloxon*).ti,ab,kw,kf. (662)
3	or/1-2 [Burpenorphine Naloxone Combo--used only for dependence treatment] (714)
4	naltrexone/ (7494)
5	BUPRENORPHINE/ (4647)
6	(anorfin* or antaxon\$ or belbuca* or bunavail* or buprenex* or buprex* or buprenorph* or buprin* or butrans*).ti,ab,kw,kf. (5778)
7	("cl 112, 302" or "cl 112302" or "cl112, 302" or "cl112302" or celupan\$).ti,ab,kw,kf. or "en 1639a".ti,ab,kw,kf,rn. or en1639a.ti,ab,kw,kf,rn. (2)
8	(finibron* or lepetan* or nalerona or nalorex or naloxon\$ or naltrel or naltrexon\$ or nemexin or nodict or nutrexon or "nih 8805").ti,ab,kw,kf. or "nih8805".ti,ab,kw,kf,rn. or norphin*.ti,ab,kw,kf. (28368)
9	(pentorel* or phaltrexia or prefin* or probuphin).ti,ab,kw,kf. (97)
10	"re via".ti,ab,kw,kf. (12)
11	regental.ti,ab,kw,kf. (1)
12	revez.ti,ab,kw,kf. (0)
13	revia.ti,ab,kw,kf,rn. (35)
14	(suboxon* or subutex* or temgesic* or transtec* or trexan or "um 952" or um952 or vivitrex or vivitrol or zubsolv*).ti,ab,kw,kf. (332)
15	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (36080)
16	exp substance-related disorders/ or exp opioid-related disorders/ or substance abuse, intravenous/ or exp substance withdrawal syndrome/ (260212)
17	(abuse* or abuser* or abusing or abused or addict* or cessation or cocain\$ or crack or crime* or criminal* or dependenc* or diamorphin* or diacetylmorphine or heroin\$ or illicit* or illegal* or "maintenance*" or misus* or (narcotic* or opioid\$ or opiat\$ or substance) or substitution\$ or user* or withdrawal* or oxycodon\$ or oxycontin\$ or oxyfast or oxyir or percolon\$ or roxicodon\$ or alcohol*).ti,ab,kw,kf. (1519857)
18	Heroin/ (5371)
19	exp Oxycodone/ (1865)
20	or/16-19 [Drug Abuse; Illegal Drugs; Addiction] (1583991)
21	3 or (and/15,20) [Naloxone-Burpen Combo OR Naltrexon & Addiciton etc] (29272)
22	(systematic adj2 (review? or overview? or scoping)).ti,ab,kw,kf. or (metaanaly\$ or meta-analy\$).pt,ti,ab,kw,kf. (209915)
23	21 and 22 (322)
24	remove duplicates from 23 (282)

MEDLINE RANDOMIZED CONTROLLED TRIAL STRATEGY [AUGUST 29, 2017]

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)		
#	Searches	Results
1	buprenorphine, naloxone drug combination/	202
2	(buprenorphin* adj3 naloxon*).ti,ab,kw,kf.	676
3	or/1-2 [Burpenorphine Naloxone Combo--used only for dependence treatment]	729

4	naltrexone/	7556
5	BUPRENORPHINE/	4681
6	(anorfin* or antaxon\$ or belbuca* or bunavail* or buprenex* or buprex* or buprenorph* or buprin* or butrans*).ti,ab,kw,kf.	5832
7	("cl 112, 302" or "cl 112302" or "cl112, 302" or "cl112302" or celupan\$).ti,ab,kw,kf. or "en 1639a".ti,ab,kw,kf,rn. or en1639a.ti,ab,kw,kf,rn.	2
8	(finibron* or lepetan* or nalerona or nalorex or naloxon\$ or naltrel or naltrexon\$ or nemexin or nodict or nutrexon or "nih 8805").ti,ab,kw,kf. or "nih8805".ti,ab,kw,kf,rn. or norphin*.ti,ab,kw,kf.	28601
9	(pentorel* or phaltrexia or pefin* or probuphin).ti,ab,kw,kf.	99
10	"re via".ti,ab,kw,kf.	12
11	regental.ti,ab,kw,kf.	1
12	revez.ti,ab,kw,kf.	0
13	revia.ti,ab,kw,kf.	35
14	(suboxon* or subutex* or temgesic* or transtec* or trexan or "um 952" or um952 or vivitrex or vivitrol or zubsolv*).ti,ab,kw,kf.	338
15	or/4-14	36371
16	substance-related disorders/ or exp opioid-related disorders/ or substance abuse, intravenous/	122054
17	(abuse* or abuser* or abusing or abused or addict* or cessation or drug dependenc* or diamorphin* or diacetylmorphine or heroin\$ or maintenance* therap\$ or opioid\$ or opiat\$ or oxycodon\$ or oxycontin\$ or oxyfast or oxyir or percolon\$ or roxicodon\$).ti,ab,kw,kf.	331667
18	Heroin/	5392
19	exp Oxycodone/	1890
20	or/16-19 [Opiate abuse]	388862
21	3 or (and/15,20) [Naloxone-Burpen Combo OR Naltrexon & Addicton etc]	27349
22	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1178916
23	exp animals/ not humans.sh.	4581839
24	22 not 23 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing]	1087253
25	(animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp\$ or cow or dog or dogs or equine or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or thoroughbred).ti. or veterinar\$.ti,ab,kw,kf,hw.	2233756
26	22 not 25 [excluding animal keywords]	1116335
27	21 and (or/24,26) [Results]	3010
28	limit 27 to yr="2015 -Current"	481
29	(2015\$ or 2016\$ or 2017\$).ed.	2988447
30	and/27,29	433
31	28 or 30	583
32	remove duplicates from 31	496

EMBASE SYSTEMATIC REVIEW STRATEGY [August 17, 2017]

1	buprenorphine plus naloxone'/de OR ((buprenorphin* NEAR/3 naloxon*):ti,ab,tn) 1523
2	anorfin*:ti,ab,tn OR belbuca*:ti,ab,tn OR buprenex*:ti,ab,tn OR buprex*:ti,ab,tn OR buprin*:ti,ab,tn OR butrans*:ti,ab,tn OR 'cl 112, 302':ti,ab OR 'cl 112302':ti,ab OR 'cl112, 302':ti,ab OR 'cl112302':ti,ab OR finibron*:ti,ab,tn OR lepetan*:ti,ab,tn OR 'nih 8805':ti,ab OR 'nih8805':ti,ab OR norphin*:ti,ab,tn OR pentorel*:ti,ab,tn OR pefin*:ti,ab,tn OR probuphin*:ti,ab,tn OR 'rx 6029 m':ti,ab OR 'rx 6029m':ti,ab OR

	rx6029m:ti,ab OR subutex*:ti,ab,tn OR temgesic*:ti,ab,tn OR transtec*:ti,ab,tn OR 'um 952':ti,ab OR um952:ti,ab 1952
3	naltrexone'/mj OR 'buprenorphine'/mj OR antaxon:ti,ab,tn OR antaxone:ti,ab,tn OR celupan:ti,ab,tn OR 'en 1639a':ti,ab,tn OR en1639a:ti,ab,tn OR nalerona:ti,ab,tn OR nalorex:ti,ab,tn OR naltrel:ti,ab,tn OR 'naltrexone':ti,ab,tn OR nemexin:ti,ab,tn OR nodict:ti,ab,tn OR nutrexon:ti,ab,tn OR phaltrexia:ti,ab,tn OR 're via':ti,ab,tn OR regental:ti,ab,tn OR revez:ti,ab,tn OR revia:ti,ab,tn OR trexan:ti,ab,tn OR vivitrex:ti,ab,tn OR vivitrol:ti,ab,tn 14555
4	bunavail*:ti,ab,tn OR buprenorphin* OR ((naloxon* NEAR/4 buprenorphin*):ti,ab,tn) OR suboxon*:ti,ab,tn OR zubsolv*:ti,ab,tn 15031
5	#2 OR #3 OR #4 23809
6	metaanaly*:ti,ab OR 'meta analy*:ti,ab OR (systematic NEAR/2 review):ti 194752
7	systematic review'/mj OR 'meta analysis'/mj 21638
8	#6 OR #7 195176
9	animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de NOT ('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de AND ('human'/exp OR 'human cell'/de)) 6279787
10	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de 2558230
11	#9 OR #10 6729613
12	narcotic dependence'/exp OR 'drug dependence'/exp OR 'oxycodone'/mj OR 'diamorphine'/mj OR 'cocaine'/mj 239400
13	abuse*:ti,ab OR abuser*:ti,ab OR abusing:ti,ab OR abused:ti,ab OR addict*:ti,ab OR cessation:ti,ab OR cocain\$ OR crack OR crime*:ti,ab OR criminal*:ti,ab OR dependenc*:ti,ab OR diamorphin*:ti,ab OR diacetylmorphine:ti,ab OR heroin\$:ti,ab OR illicit*:ti,ab OR illegal*:ti,ab OR 'maintenance*:ti,ab OR misus*:ti,ab OR narcotic* OR opioid\$ OR opiat\$ OR substance:ti,ab OR substitution\$:ti,ab OR user*:ti,ab OR withdrawal*:ti,ab OR oxycodon\$:ti,ab,tn OR oxycontin\$:ti,ab,tn OR oxyfast:ti,ab,tn OR oxyir:ti,ab,tn OR percolon\$:ti,ab,tn OR roxicodon\$:ti,ab,tn 1563071
14	alcohol*:ti,ab 383880
15	addiction'/exp OR 'drug withdrawal'/exp OR 'treatment withdrawal'/exp 424830
16	#12 OR #13 OR #14 OR #15 2024605
17	(#1 OR (#5 AND #16)) AND #8 NOT #11 289

EMBASE RCT STRATEGY [August 29, 2017]

1	abuse*:ti,ab OR abuser*:ti,ab OR abusing:ti,ab OR abused:ti,ab OR addict*:ti,ab OR cessation:ti,ab OR 'drug dependenc*:ti,ab OR diamorphin*:ti,ab OR diacetylmorphine:ti,ab OR heroin*:ti,ab OR 'maintenance* therap*:ti,ab OR opioid*:ti,ab OR opiat*:ti,ab OR oxycodon*:ti,ab OR oxycontin*:ti,ab OR oxyfast:ti,ab OR oxyir:ti,ab OR percolon*:ti,ab OR roxicodon*:ti,ab409750	409750
2	naltrexone'/mj	5634
3	buprenorphine'/mj	5545
4	naltrexon*:ti,ab,tn	7740
5	buprenorphin*:ti,ab,tn	7323
6	anorfin:ti,ab,tn,rn	2
7	buprex*:ti,ab,tn,rn	24

8	buprin*:ti,ab,tn,rn	3
9	butrans*:ti,ab,tn,rn	111
10	belbuca*:ti,ab,tn,rn	12
11	buprenex*:ti,ab,tn,rn	205
12	cl 122 302':ti,ab,tn,rn	0
13	cl122302':ti,ab,tn,rn	0
14	cl 112302':ti,ab,tn,rn	0
15	finibron*:ti,ab,tn,rn	1
16	lepetan*:ti,ab,tn,rn	17
17	pentorel*:ti,ab,tn,rn	1
18	prefin*:ti,ab,tn,rn	112
19	probuphin*:ti,ab,tn,rn	23
20	subutex*:ti,ab,tn,rn	588
21	temegestic*:ti,ab,tn,rn	4
22	transtec*:ti,ab,tn,rn	178
23	um 952':ti,ab,tn,rn	0
24	um952':ti,ab,tn,rn	0
25	antaxon*:ti,ab,tn,rn	29
26	celupan*:ti,ab,tn,rn	4
27	nalerona*:ti,ab,tn,rn	0
28	nalorex*:ti,ab,tn,rn	56
29	nalorex*:ti,ab,tn,rn	56
30	naltrel*:ti,ab,tn,rn	23
31	naltrexon*:ti,ab,tn,rn	7740
32	nemexin*:ti,ab,tn,rn	48
33	nodict*:ti,ab,tn,rn	1
34	nutrexon*:ti,ab,tn,rn	0
35	phaltrexia*:ti,ab,tn,rn	0
36	phaltresia*:ti,ab,tn,rn	0
37	re via*:ti,ab,tn,rn	18
38	regental*:ti,ab,tn,rn	1
39	revez*:ti,ab,tn,rn	3
40	revia*:ti,ab,tn,rn	294
41	trexan*:ti,ab,tn,rn	102
42	vivitrex*:ti,ab,tn,rn	21
43	viviitrol*:ti,ab,tn,rn	0
44	bunavail*:ti,ab,tn,rn	15
45	buprenorphin*:ti,ab,tn,rn	7323
46	suboxon*:ti,ab,tn,rn	562
47	zubsolv*:ti,ab,tn,rn	30
48	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47	17906
49	opiate addiction'/exp OR 'narcotic dependence'/de OR 'maintenance therapy'/mj OR 'withdrawal syndrome'/de OR 'drug craving'/de OR 'withdrawal seizure'/de OR 'drug dependence'/de OR 'drug misuse'/de	92808
50	#50((substance NEAR/2 (abus* OR addiction* OR dependenc* OR disorder*)):ti,ab) OR 'maintenance* therap*:ti,ab OR 'drug habituation':ti,ab OR toxicomani*:ti,ab	61787

51	((drug OR drugs) NEAR/2 (abus* OR addict* OR dependenc*)):ti,ab	53885
52	(narcotic* NEAR/2 (abus* OR addict* OR dependenc* OR habituation OR cessation* OR misus*)):ti,ab	1800
53	morphin*:ti,ab OR opium:ti,ab OR diamorphin*:ti,ab OR diacetylmorphine:ti,ab OR heroin*:ti,ab	78332
54	opioid*:ti,ab OR opiat*:ti,ab OR oxycodon*:ti,ab OR oxycontin*:ti,ab OR oxyfast:ti,ab OR oxyir:ti,ab OR percolon*:ti,ab OR roxicodon*:ti,ab	117438
55	#49 OR #50 OR #51 OR #52 OR #53 OR #54	310570
56	#48 AND #55	12908
57	animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de NOT ('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de AND ('human'/exp OR 'human cell'/de))	6290514
58	animal*:ti OR beaver*:ti OR beef:ti OR bovine:ti OR breeding:ti OR canine:ti OR castoris:ti OR cat:ti OR cattle:ti OR cats:ti OR chicken*:ti OR cow:ti OR dog:ti OR dogs:ti OR equine:ti OR foal:ti OR foals:ti OR fish:ti OR insect*:ti OR livestock:ti OR mice:ti OR mouse:ti OR murine:ti OR plant:ti OR plants:ti OR pork:ti OR porcine:ti OR protozoa*:ti OR purebred:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR thoroughbred:ti OR veterinar*:ti,ab,de	2561943
59	#57 OR #58	6740996
60	clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR ((clinical OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ti,ab OR placebo:ab,ti OR 'head to head':ti,ab	922711
61	#56 AND #60 NOT #59	1649
62	#61 AND (2015:py OR 2016:py OR 2017:py) AND ('Conference Abstract'/it OR 'Conference Review'/it)	119
63	#62 AND (alcohol*:ti OR pain:ti)	32
64	#62 NOT #63	87

Appendix B. Cochrane Systematic Reviews Evaluating Opioid Use Disorder Treatment Agents*

Study Reference and Search Date	Objective	Treatment Interventions	Clinical Efficacy Results	Safety Results
<p>1. <i>Minozzi et al 2014</i>⁹⁰: Detoxification treatments for opiate dependent adolescents</p> <ul style="list-style-type: none"> - Two RCTs (only one of interest) - Literature search up to January 2014 	<p>To assess the effectiveness of any detoxification treatment alone or in combination with psychosocial intervention compared with no intervention, other pharmacological intervention or psychosocial interventions on completion of treatment, reducing the use of substances and improving health and social status</p> <p><i>Participants:</i> 190 opiate dependent adolescents (13 to 18 years of age)</p>	<p>Two RCTs:</p> <ul style="list-style-type: none"> - BUP with clonidine for detoxification (1 trial: <i>Marsch 2005</i>) - BUP/NALOX maintenance for 12 weeks vs. BUP detoxification for 14 days (1 trial, 152 patients: <i>Woody 2008</i>⁸⁰) 	<p>BUP/NALOX maintenance vs. BUP detoxification (Woody 2008)</p> <p><u>Primary outcomes</u></p> <p>Drop-outs: : RR 2.67; 95% CI 1.85 to 3.86 (<i>favors maintenance treatment</i>)</p> <p>Use of substance of abuse (number of participants with opiate positive urine analysis): RR 1.03; 95% CI 0.82 to 1.28 (<i>no differences between groups</i>)</p> <p>Relapses at the end of follow-up:</p> <ul style="list-style-type: none"> - Self-reported heroin use at 12 months: RR 1.36 (95% CI 1.05 to 1.76) (<i>favors maintenance treatment</i>) - Enrollment in addiction treatment at 12 months: RR: 0.75; 95% CI 0.53 to 1.07 (trend in favor of maintenance treatment) <p><u>Secondary outcome</u></p> <p>Use of alcohol or marijuana: (no differences between groups)</p> <p>Use of cocaine: favors maintenance treatment</p>	<p><u>Secondary outcomes:</u></p> <p>Side effects: no serious AEs reported</p> <p>Most common AE: headache (16 to 21% in both groups)</p> <p>Mortality any cause: BUP/NALOX: 1 death for methadone overdose</p>

<p>2. <i>Minozzi et al 2014</i>⁸⁹: Maintenance treatments for opiate dependent adolescents</p> <ul style="list-style-type: none"> - Two RCTs (only one of interest) - Literature search up to January 2014 	<p>To assess the effectiveness of any maintenance treatment alone or in combination with psychosocial intervention compared to no intervention, other pharmacological intervention or psychosocial interventions for retaining adolescents in treatment, reducing the use of substances and improving health and social status.</p>	<p>Two RCTs:</p> <ul style="list-style-type: none"> - LAAM maintenance versus methadone maintenance (1 trial: Lehmann 1973) - BUP/NALOX maintenance for 12 weeks vs. BUP detoxification for 14 days (1 trial, 152 patients: <i>Woody 2008</i>⁸⁰) 	<p>BUP/NALOX maintenance vs. BUP detoxification (<i>Woody 2008</i>)</p> <p><u>Primary outcomes</u></p> <p>Drop-outs: : RR 0.37; 95% CI 0.26 to 0.54 (<i>favors maintenance treatment</i>)</p> <p>Use of substance of abuse (number of participants with opiate positive urine analysis): RR 0.97; 95% CI 0.78 to 1.22 (<i>no differences between groups</i>)</p> <p>Relapses at the end of follow-up:</p> <ul style="list-style-type: none"> - Self-reported heroin use at 12 months: RR 0.73; 95% CI 0.57 to 0.95 (<i>favors maintenance treatment</i>) - Enrollment in addiction treatment at 12 months: RR: 0.73; 95% CI 0.53 to 1.07 (trend in favor of maintenance treatment) <p><u>Secondary outcome</u></p> <p>Use of alcohol or marijuana: (no differences between groups)</p> <p>Use of cocaine: favors maintenance treatment</p>	<p><u>Secondary outcomes:</u></p> <p>Side effects: no serious AEs reported</p> <p>Most common AE: headache (16 to 21% in both groups)</p> <p>Mortality any cause: BUP/NALOX: 1 death for methadone overdose</p>
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<p>3. <i>Minozzi et al 2011</i>⁹⁵: Oral naltrexone maintenance treatment for opioid Dependence</p> <ul style="list-style-type: none"> - 13 studies (only one of interest) - Literature search up to June 2010 	<p>To evaluate the effects of oral naltrexone maintenance treatment versus placebo or other treatments in preventing relapse in opioid addicts after detoxification.</p>	<ul style="list-style-type: none"> - Oral naltrexone vs placebo or no pharmacological treatments - Oral naltrexone vs psychotherapy - Oral naltrexone plus psychotherapy vs BUP plus psychotherapy (<i>Schottenfield 2008</i>⁹⁶) 	<p><u>Comparison of naltrexone plus psychotherapy vs BUP plus psychotherapy</u> Retention and abstinence: RR 0.37; 95% CI 0.13-1.08 (No statistically significant difference)</p>	<p>None</p>
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* Data have been extracted from studies comparing FDA-approved products, indications and doses. Treatment interventions of interest for this report are highlighted in blue.
Abbreviations: AE, adverse event; BUP, buprenorphine; BZ, benzodiazepines; LAAM, levomethadyl acetate; NALOX, naloxone

Appendix C. Other Key Systematic Reviews Evaluating Opioid Use Disorder Treatment Agents

Study Reference and Search Date	Findings and Recommendations
1. ASAM evidence-based guideline ⁶	<ul style="list-style-type: none"> - <i>"Clinicians should consider the patient's preferences, past treatment history, and treatment setting when deciding between the use of methadone, buprenorphine, and naltrexone in the treatment of addiction involving opioid use."</i> - <i>Naltrexone is a recommended treatment in preventing relapse in opioid use disorder. Oral formula naltrexone may be considered for patients in whom adherence can be supervised or enforced.</i> - <i>There is an absence of studies that compare treatment using either oral naltrexone or extended-release injectable naltrexone versus agonist treatment with either methadone or buprenorphine.</i> <p>Areas for Further Research</p> <ul style="list-style-type: none"> - <i>More research is needed to compare the advantages of agonists and antagonists in the treatment of opioid use disorder. Whereas methadone, buprenorphine, and naltrexone are all superior to no treatment in opioid use disorder, less is known about their relative advantages.</i> - <i>Further research is needed to test the relative efficacy of extended-release injectable naltrexone as compared to agonist treatment"</i>
2. VA/DoD evidence based guideline ⁶⁰	<ul style="list-style-type: none"> - <i>"For patients with opioid use disorder, we recommend offering one of the following medications considering patient preferences:</i> <ul style="list-style-type: none"> ■ Buprenorphine/naloxone ■ Methadone in an Opioid Treatment Program (OTP) <p><i>(Buprenorphine and methadone are recommended for the treatment of OUD based on high quality evidence from multiple RCTs and meta-analyses)</i></p> <ul style="list-style-type: none"> - First-line treatment for OUD is opioid agonist treatment (OAT), methadone or buprenorphine, which can be provided in federally regulated Opioid Treatment Programs (OTPs) or through Office-based Opioid Therapy (OBOT). - Extended-release injectable naltrexone is also recommended for maintenance treatment of OUD based on moderate quality evidence - Five SRs showed that using opioid agonists for the treatment of OUD was effective in both licensed Opioid Treatment Programs (OTPs) as well as within general medical settings - Meta-analyses of studies comparing buprenorphine treatment to methadone treatment indicate that, overall, both are equivalent in terms of suppressing illicit opioid use, but that methadone has slightly better treatment retention - We found high quality evidence that buprenorphine is more effective than oral naltrexone or placebo therapy in improving opioid consumption and time to relapse [Schottenfeld 2008] - We found high quality evidence supporting buprenorphine for maintenance (14 weeks) over taper (four weeks) for improving treatment retention and moderate quality evidence supporting buprenorphine for improving opioid consumption outcomes. - Several studies have shown that buprenorphine can be used successfully in pregnancy. - Based on the available evidence, oral naltrexone cannot be recommended for treatment of OUD.[175-177] There is insufficient evidence of efficacy of oral naltrexone, and the staff time that is associated with observing and monitoring medication adherence must be taken into consideration when making the decision to use oral naltrexone"

Abbreviations: AE, adverse event; ASAM, American Society of Addiction Medicine ; BUP, buprenorphine; NALOX, naloxone; OUD, opioid use disorder; VA/DoD, Veteran Affairs/Department of Defense

Appendix D. Randomized Controlled Trials Evaluating Opioid Use Disorder Treatment Agents

Reference /Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
<p>1. Webster et al 2016⁹¹</p> <p>Randomized, active-controlled, non-inferiority study conducted from June 2013 to January 2014</p> <p>Setting: 13 sites in the United States</p>	313	Males and females aged 18 to 65 years who met clinical criteria for opioid dependence in the past 12 months based on the DSMIV-TR.	<p>Sublingual, rapidly dissolving BNX tablet (Zubsolv) or generic BUP</p> <p><u>Phase I:</u> blinded induction phase on days 1 and 2:</p> <p>Day 1:</p> <ul style="list-style-type: none"> - BNX: 5.7/1.4 mg - BUP: 8 mg <p>Day 2:</p> <ul style="list-style-type: none"> - BNX: 5.7/1.4 or 11.4/2.8 mg - BUP: 8 or 16 mg <p><u>Phase II:</u> open-label stabilization and early maintenance phase (days 3 through 28): all patients received BNX 5.7/1.4 or 11.4/2.8 mg</p>	<p>Induction phase: BNX vs BUP</p> <p><u>Primary endpoint:</u></p> <p>Treatment retention at day 3 (Non-inferiority when lower limit of the 95% CI $\geq 10\%$ in the % of patients retained in treatment):</p> <p><u>Pre protocol assessment:</u></p> <p>BUP: 122/128 (95.3%) BNX: 113/128 (88.3%) 95% CI: -13.7, -0.4; p= 0.040 (Lower limit of 95% CI= - 13.7 → Non-inferiority not demonstrated. More patients retained at day 3 with BUP than BNX)</p> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> - Opioid withdrawal symptoms and cravings (COWS, SOWS and VAS): Comparable results between groups 	<ul style="list-style-type: none"> - Most common AEs: nausea, headache (Similar incidence between groups) - 3 discontinuations due to AEs - No deaths
<p>2. Mokri et al 2016⁹⁷</p> <p>12-week single-site, two-group parallel randomized double-blind clinical trial</p> <p>Setting: Tehran, Iran</p>	102	Volunteers meeting DSM-IV-TR criteria for opioid dependence. All study participants underwent medically assisted detoxification	<p>Oral NTX (n = 51) or sublingual BNX (n = 51)</p> <p>All patients received drug counseling</p> <p>Duration: 12 weeks</p>	<p><u>Primary endpoint:</u></p> <ul style="list-style-type: none"> - Mean number of days of opioid abstinence (urine toxicology tests): 28.8 (95% CI 20.0–37.5) with BNX 21.6 (95% CI 14.4–28.7) with NTX (<i>P</i> = 0.205) <p><u>Secondary endpoint:</u></p> <ul style="list-style-type: none"> - Mean number of opioid-negative urine tests: 19.7 (95% CI 17.7–21.6) with BNX 15.4 (95% CI 13.1–17.8) with NTX (<i>P</i> = 0.049) - Mean number of days in treatment retention: 70.6 (95% CI 63.6–77.7) with BNX versus 56.5 (47.8–65.3) with NTX (<i>P</i> = 0.013). - % patients with sustained, verified opioid-abstinence for 12 weeks: 16% (8/51) in the BNX group 8% (4/51) in the NTX group (<i>P</i> = 0.219). - % retention at week 12 and 24: 71% at 12 weeks and 39% at 24 week with BNX 40% at 12 weeks and 2% at 24 week with NTX (The number of opioid negative tests and treatment retention were higher in the BNX group) 	<ul style="list-style-type: none"> - 5 patients required protective transfer (2 in NTX group, 3 in BNX group) - 3 patients died of drug overdose (2 in NTX group, 1 in BNX group) - Aggression, violence, impulsivity, self-injury or criminal justice involvement: 33% in BNX group and 27% in NTX group had at least one of these AEs

Reference /Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
<p>3. Gunderson et al 2016⁹³</p> <p>Switching study</p> <p>Multicenter, prospective, randomized, parallel-group non-inferiority trial (ISTART study) conducted from August 2013 to April 2014</p> <p>Setting: 43 sites in the United States</p>	287	Adults aged 18 to 65 years who met the criteria for opioid dependence (DSM-IV-TR) and had at least mild withdrawal symptoms	<p>Induction phase: D 1 to D 3 BNX sublingual tablet (Zubsolv, higher bio-availability formulation) vs generic buprenorphine</p> <p>Stabilization phase: D 3 to D 15 BNX sublingual tablet vs BNX sublingual film</p> <p>Switching phase: D 15 to D 22 Patients switched from BNX sublingual tablet to BNX sublingual film and viceversa</p>	<p>Switching phase: (287 out of 758 switched from BNX tablets to film)</p> <p><u>% of withdrawals at day 15:</u> 8.7% with BNX film 6.1% with BNX tablet</p> <p><u>Opioid withdrawal and cravings at day 15 and 22:</u> similar between groups</p> <p><u>Preference ratings at day 22:</u> favored BNX tablet for taste, mouth-feel, ease of administration and overall preference (p< 0.0001)</p>	<p>Treatment related AEs 8.3% with BNX tablet 7.5% with BNX film</p> <p>No treatment-related serious AEs</p>
<p>4. Gunderson et al 2015⁹²</p> <p>Multicenter, prospective, randomized, parallel-group non-inferiority trial (ISTART study) conducted from August 2013 to April 2014</p> <p>Setting: 43 sites in the United States</p>	758	Adults aged 18 to 65 years who met the criteria for opioid dependence (DSM-IV-TR) and had at least mild withdrawal symptoms	<p>Induction phase: D 1 to D 3 BNX sublingual tablet (Zubsolv, higher bio-availability formulation) vs generic buprenorphine</p> <p>Stabilization phase: D 3 to D 15 BNX sublingual tablet vs BNX sublingual film</p> <p>Switching phase: D 15 to D 22 Patients switched from BNX sublingual tablet to BNX sublingual film and viceversa</p>	<p>Induction and stabilization phase <u>Co-Primary endpoint:</u> Treatment retention at day 3 and 15 (Non-inferiority when lower limit of the 95% CI $\geq 10\%$ in the % of patients retained in treatment):</p> <ul style="list-style-type: none"> Day 3 retention rate: (induction phase) 93.9% (309/329) with BNX tablet 92.6% (302/326) with BUP (between-group difference 95%CI, -2.6 to 5.1). Lower limit of 95% CI= - 2.6 → Non-inferiority was demonstrated Day 15 retention rate: (stabilization phase) 83.0% (273/329) with BNX tablet 82.5% (269/326) with BNX film (between-group difference 95% CI, -5.3 to 6.3)→ Non-inferiority was demonstrated 	Safety profile was similar between the three groups

Reference /Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
<p>5. <i>Rosenthal et al 2016</i>⁹⁴</p> <p>Randomized, double-blind, double-dummy, active controlled, 26-week, multisite study conducted from June 26, 2014 to May 18, 2015</p> <p>Setting: 21 US sites</p>	177	Patients with primary diagnosis of opioid dependence, aged 18 to 65 years, received sublingual buprenorphine for at least 24 weeks as an outpatient at a stable dosage of 8 mg/d or less, and showed no evidence of opioid withdrawal or illicit opioid-positive urine samples for at least 90 days prior to study entry	<p>Buprenorphine implant (BUP implant)</p> <p>Sublingual buprenorphine (SL BUP)</p>	<p><u>Primary endpoint:</u></p> <ul style="list-style-type: none"> - Difference in % of responders, defined as participants with at least 4 of 6 months without evidence of illicit opioid use (based on urine test and self-report composites) (Non-inferiority established for a lower bound of the 95% CI > -0.20 within the ITT population [1-sided testing with a significance threshold of $p < .025$]. Superiority analysis were 2-sided with a significance threshold of $p < .05$) <p>81/84 participants (96.4%) with BUP implant 78/89 participants (87.6%) with SL BUP Difference=8.8% (1-sided 97.5%CI, 0.009 to ∞; $p < 0.001$ for NI; $P = 0.03$ for superiority)</p> <p><u>Secondary endpoints:</u></p> <ul style="list-style-type: none"> - Cumulative abstinence of illicit opioid use at M 6: 85.7% with BUP implant vs 71.9% with SL BUP (hazard ratio, 13.8; 95% CI, 0.018-0.258; $P = .03$) - Time to first illicit opioid use: longer with BUP implant than SL BUP - Craving and withdrawal symptoms: no significant differences between groups 	<ul style="list-style-type: none"> - SAEs: 5 participants (3 with SL BUP, 2 with BUP implant) - Discontinuations: 1 in BUP implant group due to muscle spasms - Incidence of local AEs: higher with BUP implant - 1 accidental pediatric tablet exposure - No implant migration cases
<p>6. <i>Ahmadi et al 2003</i>⁹⁸</p> <p>Three-group, randomized, controlled study</p>	204	Intravenous-buprenorphine-dependent patients who met the DSM-IV criteria for opioid dependence	<p>Oral methadone 50 mg vs oral naltrexone 50 mg</p> <p>Sublingual buprenorphine tablet 5 mg vs oral naltrexone 50 mg</p> <p>Sublingual buprenorphine tablet 5 mg vs oral methadone 50 mg</p> <p>Duration: 24-week treatment period</p>	Retention in the 5-mg oral buprenorphine group was significantly better than in the 50-mg naltrexone dose group ($p = 0.000$).	Subjects did not report any significant side-effects while taking oral methadone, sublingual buprenorphine or oral naltrexone

Abbreviations: AE, adverse event; BUP, buprenorphine; CI, confidence interval; COWS, Clinical Opiate Withdrawal Scale; D, day; DSM, diagnostic and statistical manual of mental disorders, fourth edition, text revision; ITT, intention-to-treat; NALOX, naloxone; BNX; buprenorphine/naloxone; NTX, naltrexone; SOWS, Subjective Opiate Withdrawal Scale; VAS; visual analogue scale

Appendix E. List of Excluded References

Wrong comparator
<ol style="list-style-type: none"> 1. Crowley D, Van Hout MC, Author A, et al. Effectiveness of pharmacotherapies in increasing treatment retention and reducing opioid overdose death in individuals recently released from prison. A systematic review. <i>Heroin Addiction and Related Clinical Problems</i> 2017 192 25-42 Date of Publication 1 Apr 2017. 2. Davids E, Gastpar M. Buprenorphine in the treatment of opioid dependence. <i>European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology</i>. 2004;14(3):209-216. 3. Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. <i>Canadian family physician Medecin de famille canadien</i>. 2012;58(1):37-41. 4. Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. <i>The Cochrane database of systematic reviews</i>. 2017;2(100909747):CD002025. 5. Johansson BA, Berglund M, Lindgren A. Efficacy of maintenance treatment with naltrexone for opioid dependence: a meta-analytical review. <i>Addiction (Abingdon, England)</i>. 2006;101(4):491-503. 6. Kirchmayer U, Davoli M, Verster A. Naltrexone maintenance treatment for opioid dependence. <i>The Cochrane database of systematic reviews</i>. 2003(2):CD001333. 7. Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri A, Perucci CA. A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. <i>Addiction (Abingdon, England)</i>. 2002;97(10):1241-1249. 8. Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. <i>CNS neuroscience & therapeutics</i>. 2011;17(6):629-636. 9. O'Shea J, Law F, Melichar J. Opioid dependence. <i>BMJ clinical evidence</i>. 2007;2007(101294314). 10. O'Shea J, Law F, Melichar J. Opioid dependence. <i>BMJ clinical evidence</i>. 2009;2009(101294314). 11. Perry AE, Neilson M, Martyn-St James M, et al. Pharmacological interventions for drug-using offenders. <i>The Cochrane database of systematic reviews</i>. 2015(6):CD010862. 12. Praveen KT, Law F, O'Shea J, Melichar J. Opioid dependence. <i>BMJ clinical evidence</i>. 2011;2011(101294314). 13. Roozen HG, de Waart R, van der Windt DAWM, van den Brink W, de Jong CAJ, Kerkhof AJFM. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. <i>European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology</i>. 2006;16(5):311-323. 14. Soyka M, Kranzler HR, van den Brink W, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence. <i>The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry</i>. 2011;12(3):160-187. 15. Sullivan MA, Bisaga A, Glass A, et al. Opioid use and dropout in patients receiving oral naltrexone with or without single administration of injection naltrexone. <i>Drug Alcohol Depend</i>. 2015;147:122-129. 16. Van Den Brink W, Haasen C, Author A, et al. Evidence-based treatment of opioid-dependent patients. <i>Canadian Journal of Psychiatry</i> 2006 5110 635-646 Date of Publication September 2006.
Not a systematic review/not a RCT
<ol style="list-style-type: none"> 17. Kahan M, Srivastava A, Ordean A, Cirone S. Buprenorphine: new treatment of opioid addiction in primary care. <i>Canadian family physician Medecin de famille canadien</i>. 2011;57(3):281-289.
Wrong outcome
<ol style="list-style-type: none"> 18. Carter J, Dammerman R, Frost M, et al. Health economics of probuphine vs. Oral buprenorphine, injectable naltrexone, or methadone for opioid dependence. <i>American Journal on Addictions</i> 2017 263 293 Date of Publication 1 Apr 2017. 19. Helm S, Trescot AM, Colson J, Sehgal N, Silverman S. Opioid antagonists, partial agonists, and agonists/antagonists: the role of office-based detoxification. <i>Pain physician</i>. 2008;11(2):225-235.